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PATHOLOGIC PHYSIOLOGY IN SOME DISTURBANCES OF CARBOHYDRATE METABOLISM

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IN A Harvey lecture given ten years ago, Carl Cori described what was then known about the metabolism of glucose and developed the diagram in Fig. 1 which soon became known as the Cori Simplified Scheme of Carbohydrate Metabolism. As a guide to the understanding and the clinical teaching of disturbances of carbohydrate metabolism, I have found the diagram most useful, and the passing of time, with acquisition of further knowledge, has in no way changed the original concept. Gaps have merely been filled in. In the slight modification of the original diagram (Fig. 2), I have attempted to pin point the areas of special clinical significance and with it I shall try to review for you the more interesting and important problems.

AREA 1. INITIAL GLUCOSE METABOLISM

In Area 1 lies the main defect in *diabetes mellitus*. Here glucose first enters the cycle by becoming phosphorylated at carbon No. 6, as depicted in the reaction in Fig. 3. The specific enzyme concerned is hexokinase, perhaps now better referred to as glucokinase, which is widely distributed in the body, and which requires the presence of adenosine triphosphate (ATP) as the source of energy and magnesium as a catalyst. Anterior pituitary and adrenal cortical hormones inhibit the reaction while insulin acts to remove such inhibition. In the original Cori diagram, the reaction is indicated as proceeding only one way. Recently Najaar and Gamble proved it to be an equilibrium reaction with the point of equilibrium shifted far toward glucose-6-phosphate. It is now well accepted that diabetes mellitus can be produced either by creating a deficiency of insulin or an excess of anterior pituitary or adrenal cortical effect, and ameliorated by reversing the situations. The clinical train of events which follows the persistent inhibition of the glucokinase reaction is shown in Fig. 4.

The over-all, long-term course taken by most juvenile diabetics is extraordinarily predictable, and for that reason I would like to say a few words about it. It may be diagramed as illustrated in Fig. 5. The onset

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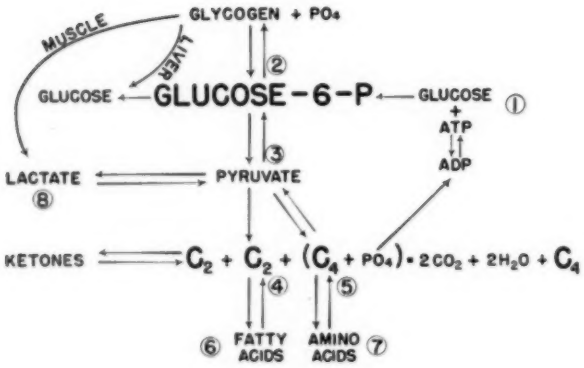

CORI SIMPLIFIED SCHEME OF CARBOHYDRATE METABOLISM

Fig. 1.

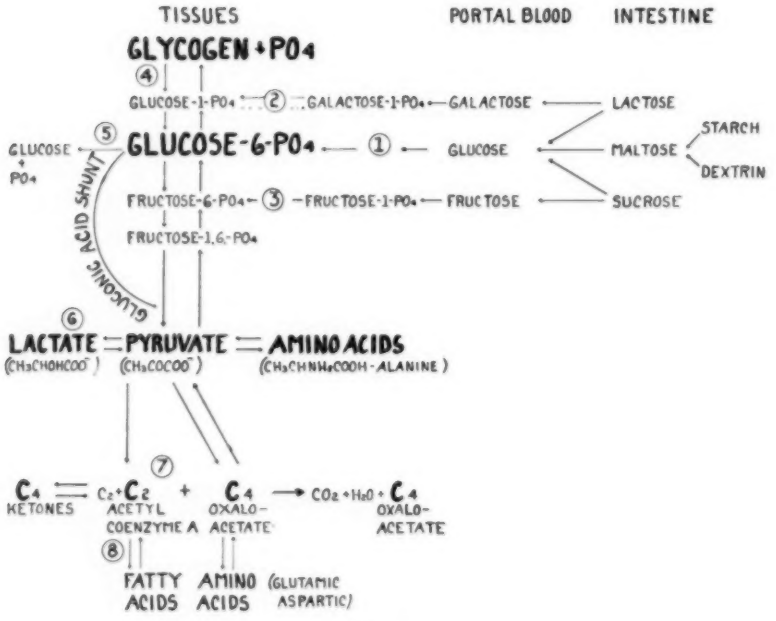

Fig. 2.

may occur at any time and may very well be an alloxan-like injury of the β cells as postulated by Lazarow. After a short period of mildness, there usually occurs a period of rapid progression to the stage of total diabetes. It is during this period, coverbe avoided. The recovery in some 10 per cent of all children continues to the point where exogenous insulin may not be required. The duration of such initial recovery, however, is likely to be short, lasting but a few days, weeks, or, occasionally, months.

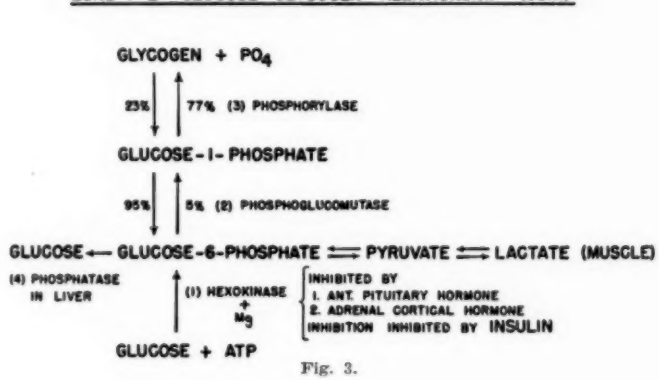

Fig. 3.

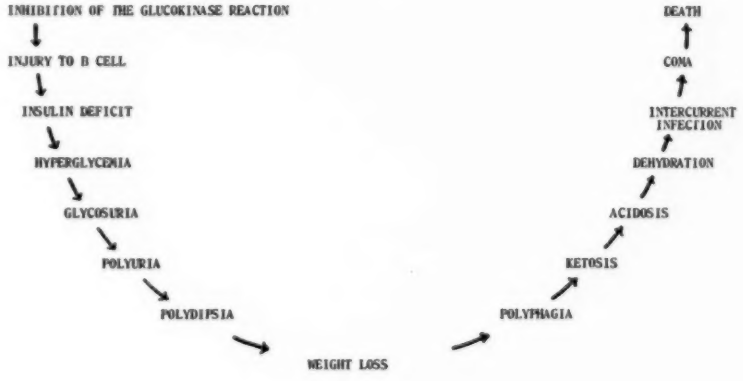

Fig. 4.

ing usually only a few weeks or months, that the clinical train of events just pictured is to be seen. With good treatment, temporary recovery, sometimes very rapid and remarkable, should be anticipated, or else repeated severe, and sometimes disastrous, insulin reactions may not Then, subsequent loss of tolerance occurs apparently as part of the natural course of the disease, characterized usually by a succession of sharp dips and partial, incomplete recoveries until after a few years a state of total or near-total diabetes is again to be seen, this time permanently. Factors

precipitating the secondary losses of tolerance are such as to stimulate insulin secretion and further expose the beta cells to alloxan injury according to the Lazarow concept, until perhaps all are rendered functionless, with little or no possibility of subsequent recovery. Some semblance of quantitation can be added to such a concept by plotting the apparent metabolic glucose:insulin ratio on the ordinate against time on the abscissa. The G:I ratio is obtained as follows:

$$\frac{\text{Metabolic Glucose: Insulin Ratio Equals Total Available Glucose-Urinary Glucose}}{\text{Insulin}}$$

During ketosis and acidosis it is always to be found near the base line (1.5 to 2.0), and after some years almost never exceeds 10 or is less than 1.5.

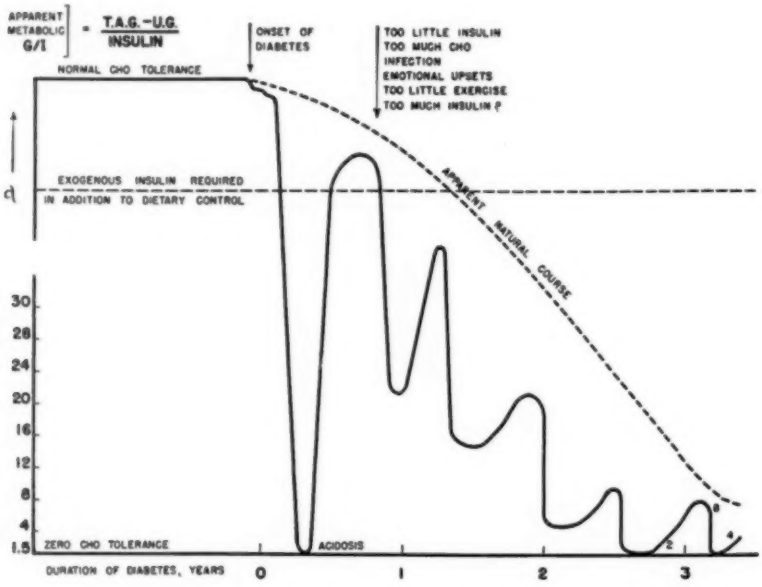

Fig. 5.—(From Hartmann, Sr., Wohltmann, and Hartmann, Jr.: J. PEDIAT., 1954.)

AREA 2. GALACTOSE METABOLISM (FIG. 2)

In Area 2 are to be found the steps which are required for the entrance of galactose into the glucose cycle. The details are pictured in Fig. 6. In especially the liver, kidney, and intestine, galactose first reacts with ATP under the influence of specific galactokinase with formation of galactose-1-PO_4. Then with the assistance of the enzyme galacto-waldenase and the coenzyme uridine-diphosphateglucose (UDPG), galactose-1-PO_4 is converted to glucose-1-PO_4, which is in equilibrium with glucose-6-PO_4 as previously indicated in the original Cori cycle.

For many years it has been known that diseases of the liver were likely to be associated with impaired metab-

olism of galactose, and the galactose tolerance test was found frequently of value in the clinical evaluation of liver function. Of much greater significance was the discovery some twenty years ago by Mason and Turner, that an isolated specific impairment of metabolism of galactose could also occur, which was congenital and sometimes familial, and of the greatest consequence. Infants inheriting its most severe form would shortly after birth exhibit signs of nutritional failure characterized by anorexia and weight loss, would develop enlargement of the liver, sometimes with jaundice and ascites, and later cirrhosis, would show sugar in their urine and hyperglycemia, and, most significantly, develop cataracts and become severely mentally retarded. It was while studying such an infant a few years ago that an incident occurred which reawakened my interest in blood sugar. During

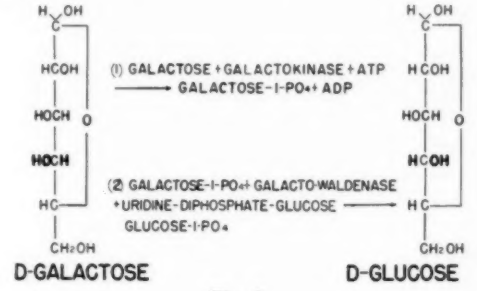

Fig. 6.

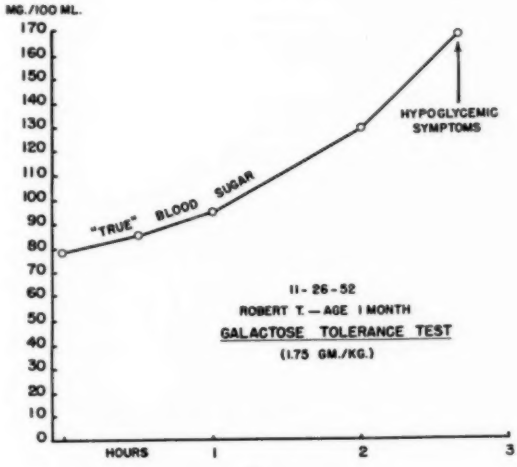

Fig. 7.

the galactose tolerance test the infant collapsed in a manner quite typical of hypoglycemia and was promptly revived by intravenous glucose. Blood sugar values obtained by the Somogyi modification of the Shaffer-Hartmann method, which allowed only "true-

sugar'' to be determined, were as shown in Fig. 7. Because of the nature of the circumstances, it seemed reasonable to conclude that the ''true sugar'' determined was largely galactose, and that as it rose, glucose must have fallen to a level consistent with severe hypoglucemic symptoms. A subsequent repetition of the galactose tolerance test, with separation of glucose from galactose in the blood determinations, verified our assumptions, although on this occasion no severe symptoms accompanied the considerable hypoglucemia of 16 mg. per 100 ml. (Fig. 8). The questions that then naturally arose were: ''Are there other situations where hypoglucemia might be masked by galactosemia?'' and ''What are the concentrations of blood galactose in infants and children under usual and unusual circumstances?''

It will perhaps be more interesting to tell the story in the way it was unfolded. By first concentrating on infants on simple diets where ingested carbohydrate necessarily had to be absorbed as either glucose or galactose, normal blood values for the two sugars were rather simply obtained by first determining blood sugar in toto and then again after glucose was removed by yeast fermentation, the residual sugar being considered galactose.

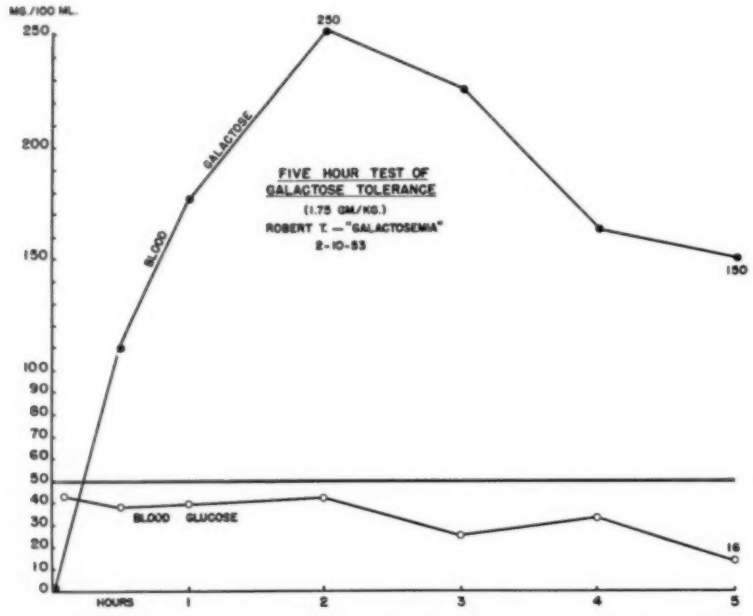

Fig. 8.—(From Hartmann, Grunwaldt, and James, Jr.: J. PEDIAT., 1953.)

For values obtained from random sampling of normal or near-normal milk-fed infants, see Table I. It is to be noted that occasionally as much as 40 per cent of the total blood sugar was galactose.

In milk-allergic but otherwise normal nonmilk-fed infants with no lactose in their formulas and in newborn infants before feeding, blood galactose values were zero, as anticipated, lending confidence in the method (Table II).

In infants resuming milk feedings after protracted therapeutic underfeeding, and complete milk restriction from their diets, because of persistent severe diarrhea, the situation was often quite different. Hypergalactosemia, sometimes actual, sometimes only relative, and severe hypoglucemia were frequently observed (Table III). Our previous experiences with such infants, where clini-

TABLE I. DETERMINATION OF THE RANGE OF GALACTOSE CONCENTRATIONS IN CAPILLARY WHOLE BLOOD AND VENOUS SERUM IN A VARIETY OF NONACUTELY ILL INFANTS RECEIVING REGULAR MILK FEEDINGS

INFANT	AGE (MO.)	DIAGNOSIS	TRUE GLUCOSE (MG./100 ML.)	GALACTOSE (MG./100 ML.)	GALACTOSE / TOTAL × 100
Determinations made shortly after feeding					
Linda W.	7	Umbilical hernia	45.7 65.8	31.3 13.0	40.5* 16.5
Michael W.	3	Cleft palate	55.3 47.8	26.0 31.9	32.0* 40.0
Sherman J.	4	G.U. anomaly	55.3	26.0	32.0*
Bonnie F.	4	Cleft palate	34.6	26.0	37.0
James P.	2	Jaundice	51.2	31.0	38.2
Lloyd W.	1½	Hemangioma	68.3	3.9	5.4
Determinations made about 3 hours after feeding					
Donald P.	10	G.U. anomaly	63.0	0.0	0.0
Lena K.	2	Cleft palate	54.9	3.9	6.6

*Determinations on venous serum.

From Hartmann, Grunwaldt, and James, Jr.: J. PEDIAT., 1953.

TABLE II. DETERMINATION OF THE RANGE OF GALACTOSE CONCENTRATIONS IN CAPILLARY WHOLE BLOOD IN NONACUTELY ILL INFANTS RECEIVING NO MILK OR LACTOSE-CONTAINING FOOD

INFANT	AGE (MO.)	DIAGNOSIS	TRUE GLUCOSE (MG./100 ML.)	GALACTOSE (MG./100 ML.)	GALACTOSE / TOTAL × 100
Geoffrey G.	4	Allergy (on Nutramigen)	75.0	0.0	0.0
Baby R.	Newborn	Diabetic mother	23.8	0.0	0.0
Ronald L.	2½	Bronchiolitis (on Mull-Soy)	58.0	0.0	0.0
Robert T.	1	Galactosemia (on Mull-Soy)	29.2	7.8	21.0
			59.1	3.9	6.3
			82.0	3.9	4.0
			63.7	13.5	17.5

From Hartmann, Grunwaldt, and James, Jr.: J. PEDIAT., 1953.

TABLE III. DETERMINATION OF THE RANGE OF GALACTOSE CONCENTRATIONS IN CAPILLARY WHOLE BLOOD OF INFANTS TREATED FOR DIARRHEA BY STARVATION OR UNDERFEEDING

INFANT	AGE (MO.)	TIME	TRUE GLUCOSE (MG./100 ML.)	GALACTOSE (MG./100 ML.)	GALACTOSE / TOTAL × 100
Laritta I.	2	On lactic acid milk	0.0	25.0	100.0
	2½	On lactic acid milk	54.9	7.8	12.4
	3	On Alacta	54.9	3.9	6.6
Gary S.	4	On lactic acid milk	20.0	30.0	60.0
		On lactic acid milk	26.5	22.0	45.5
Lilly S.	2	On D.A.S.*	22.2	7.8	35.0

*Dextrose-Amigen-Salt.

cally typical hypoglycemic reactions were frequently encountered, some with the expected low blood sugar values but others with blood sugars questionably compatible with severe symptoms, led us to anticipate just such explanatory findings. A situation typical of many others is shown in Fig. 9. Somewhat similar situations have been seen in surgical cases unable to be fed adequately for extended periods.

We next began to wonder about the cause of some of the unexplained periods of hypothermia, cyanosis, and feeble respiration, occurring in prematures without diagnosable injury or disease, some of whom eventually recovered and developed in a normal fashion. We soon had an opportunity to make blood sugar observations in such a premature (Table IV). Here, during the early neonatal period when no glucose or its precursor was added

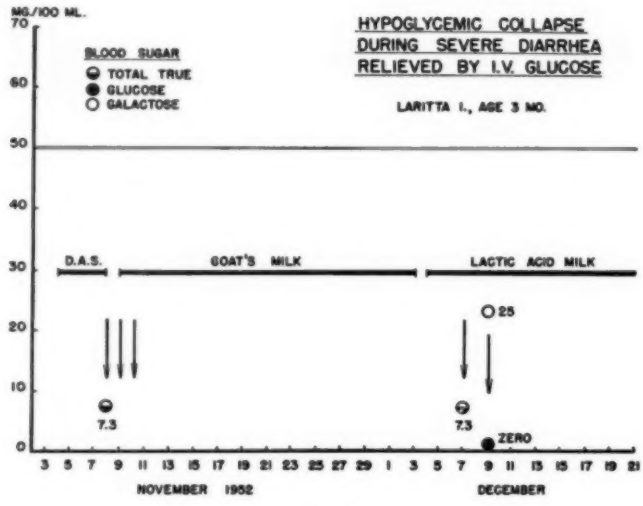

Fig. 9.

TABLE IV. PREMATURE INFANT C., BORN OCT. 30, 1953, WEIGHT 1.29 KILOGRAMS

DATE	TIME	WHOLE BLOOD—MG./100 ML. GALACTOSE	GLUCOSE	"TOTAL"	REMARKS
11/ 7/53	3:00 P.M	--	--	34	Clinical picture: On 11/7/53 a sudden attack of cyanosis and cessation of respiration, requiring resuscitation measures. Subnormal temperature from 10/31/53 to 11/10/53. Gastric tube and subcutaneous feedings required.
	8:00 P.M.	0	0	0	
11/ 9/53	10:00 A.M.	13	8	18	
	6:00 P.M. (before feeding)	8	0	6	
	45 min. after feeding	29	8	23	
11/10/53	10:30 P.M.	41	22	54	General improvement. Steady gain in weight. No untoward symptoms, but feeding still by tube
11/20/53	Before feeding	22	46	64	
	1 hr. after feeding	20	81	97	

to the diluted milk feeding, significant hypoglucemia with both actual and relative hypergalactosemia was noted, the hypoglucemia being corrected by Dextri-Maltose addition to the formula, and the hypergalactosemia spontaneously disappearing.

The question which then arose was: "In the diarrheal infants showing transiently reduced galactose tolerance, was the cause the protracted re-

TABLE V. GALACTOSE TOLERANCE TEST (1.75 GM./KG. ORALLY) IN JOHNNIE A. AFTER A YEAR OF NO MILK IN DIET

TIME	WHOLE BLOOD—MG./100 ML.	
	GALACTOSE	GLUCOSE
Fasting	0	74
½ hr.	9	73
1 hr.	7	91
2 hr.	9	94
3 hr.	0	69

ing their in utero existence, also showed normal ability to handle the

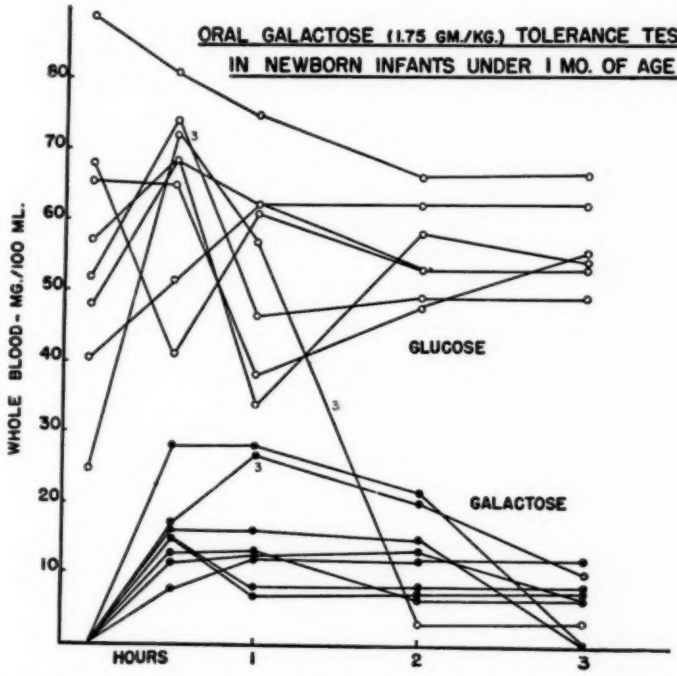

Fig. 10.—(From Hartmann, McCoy, Swarm, and Nakasato: J. PEDIAT., 1954.)

moval of milk and other sources of galactose, or something else?"

A galactose tolerance test in a milk-allergic infant without milk in the diet for more than a year showed a normal response (Table V).

Newborn infants, presumably not required to metabolize galactose dur-

sugar (Fig. 10). Some other cause must therefore exist to explain the deficiency. Perhaps the severe malnutrition in the very young is associated with enzyme or coenzyme depletion and is the cause.

Occasionally the occurrence of an acute infectious diarrhea without pro-

tracted starvation can lead to reduced galactose tolerance and confusion, as illustrated by the following situation:

A young boy, 22 months old, previously in good health and nutrition, became acutely ill with fever, vomiting, and diarrhea (Table VI). Acute bacillary dysentery was suspected. After a short period of total food restriction, milk was allowed which he took in large quantities. Because of administered, following which drowsiness became marked stupor. A check on the blood sugar revealed it to be 196 mg. per 100 ml. It was at this time that he was brought to the St. Louis Children's Hospital, about 3:30 in the morning. I suspected what was going on and requested that no more insulin be administered but instead blood be obtained for both glucose and galactose, and that the boy be given I.V. glucose, if found hypo-

TABLE VI. EDWARD B., 22 MONTHS OF AGE
AFTER THREE DAYS OF FEVER, VOMITING, AND DIARRHEA

DATE	TIME	TOTAL	MG./100 ML. WHOLE BLOOD SUGAR		MG./100 ML. SPINAL FLUID SUGAR		URINE SUGAR	REMARKS
			GALACT.	GLUCOSE	GALACT.	GLUCOSE		
3/1/54	7 P.M.	232					+	Drowsy. Given 25 units insulin
	11 P.M.	196					+	Comatose. Sent to St. Louis Children's Hospital
3/2/54	4 A.M.	62	56	6	16	19	–	CO_2 cont. 9.1 meq./L. Cl 139 1/6 M. Na-lactate given
	8:30 A.M.	15	0	15	24	0	–	CO_2 cont. 21.6 meq./L. I.V. glucose given

TABLE VII. ROGER N., BORN SEPT. 22, 1953

DATE	TIME	WHOLE BLOOD— MG./100 ML.		SPINAL FLUID— MG./100 ML.		URINE— MG./100 ML.
		GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE
9/24/53		42	46			
9/26/53		127	31			
9/28/53	Before galactose	163	46			
	45 min. after	272	67			
	60 min. after	325	25			
	120 min. after	320	46			
	180 min. after	298	88			6,780
9/29/53		115	68	114	21	
9/30/53	8 A.M.	20		17		136
	2:30 P.M.					118
10/ 2/53		12	67	10		
10/14/53		0	57			

drowsiness and some hyperventilation at the height of the febrile illness suggestive of acidosis and because of the presence of diabetes mellitus in the mother, the occurrence of that disease was feared. A urine examination revealed sugar and a blood sugar was found to be 232 mg. per 100 ml. Twenty-five units of insulin was then

glucemic, after 1/6 M Na-lactate solution was given for the dehydration and acidosis. This was done and he promptly awakened and improved, and subsequent events revealed that he did not have diabetes mellitus but instead a transient galactose diabetes associated with the infection and consumption of a large quantity of milk

Insulin administration apparently had caused an already low blood glucose concentration to fall to such a level that insulin coma resulted, and complicated the diarrheal acidosis and dehydration.

During some of our studies on galactose metabolism we had occasion to study urine, and noted that the renal threshold for galactose was much lower than for glucose and quite high urinary concentrations of galactose occurred during moderate galactosemia (as occurs during the tolerance test), the spinal fluid values remain much lower than those of the blood.

In one child with jaundice, probably on the basis of hepatic cirrhosis, galactosemia (Table VII). In this child it is also to be noted that in the presence of the persistent severe congenital type of galactosemia the cerebrospinal fluid showed concentrations of galactose identical with those of the blood. In acute transient galacto-

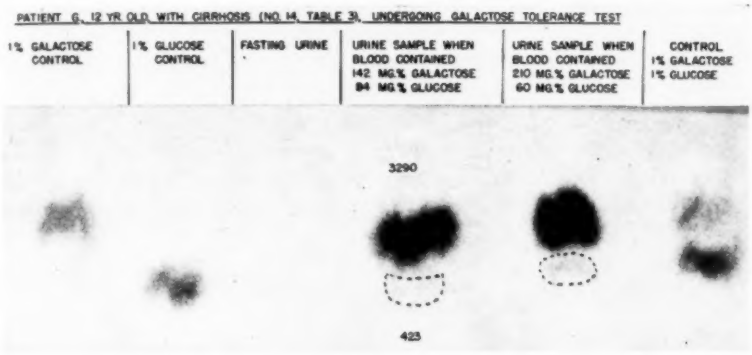
PATIENT G, 12 YR OLD WITH CIRRHOSIS (NO. 14, TABLE 3), UNDERGOING GALACTOSE TOLERANCE TEST
1% GALACTOSE CONTROL
1% GLUCOSE CONTROL
FASTING URINE
URINE SAMPLE WHEN BLOOD CONTAINED 142 MG.% GALACTOSE 84 MG.% GLUCOSE
URINE SAMPLE WHEN BLOOD CONTAINED 210 MG.% GALACTOSE 60 MG.% GLUCOSE
CONTROL 1% GALACTOSE 1% GLUCOSE
3290
423

Fig. 11.

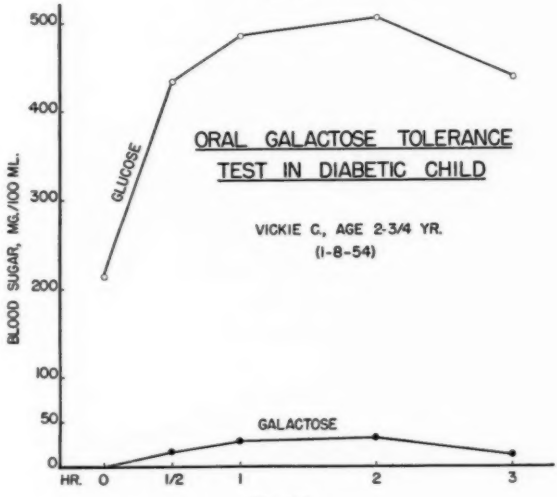

Fig. 12.

galactosemia, which appeared during a galactose tolerance test, was accompanied not only by galactosuria, but also by glucosuria, despite a blood concentration of glucose much below the normal threshold (Fig. 11).

A galactose tolerance test made when a severe diabetic child was without insulin effect indicates how quickly galactose can enter the glucose cycle, and, after dephosphorylation of glucose-6-PO_4, can become unutilizable free glucose (Fig. 12). The galactose tolerance test in this diabetic child closely resembles the typical diabetic glucose tolerance test.

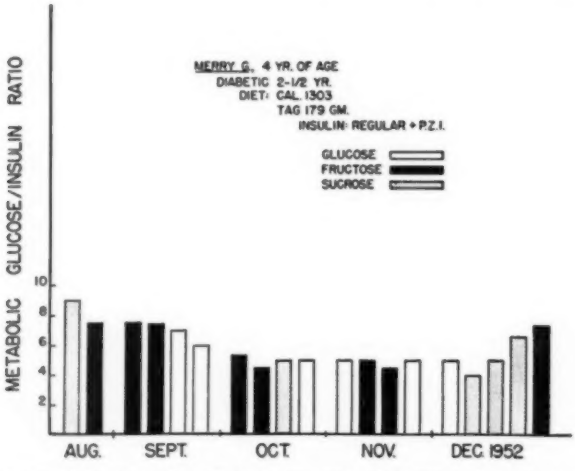

Fig. 13.—(From Hartmann, Sr., Wohltmann, and Hartmann, Jr.: J. PEDIAT., 1954.)

AREA 3. FRUCTOSE METABOLISM (FIG. 2)

Fructose enters the glucose cycle as a result of a reaction between fructose and ATP and the enzyme fructokinase which leads first to the formation of fructose-1-PO_4 and then either directly, as postulated by Cori, to fructose-6-PO_4 which is in equilibrium with glucose-6-PO_4, or, first, as thought by Leuthardt, to dihydroxy acetone phosphate and glyceraldehyde, with subsequent condensation of triose phosphate to hexose diphosphate and then to fructose-6-phosphate. The better initial utilization of fructose than glucose by the diabetic animal is to be explained by the fact that insulin is not required for any of the above reactions. Why, in the presence of an adequate supply of insulin, there should be any superiority of fructose over glucose in regard to antiketogenesis and lipogenesis is not so clear.

The remote effect of feeding fructose to the diabetic child is clearly, however, noninsulin-sparing and exactly that of feeding glucose, as noted in some of our recent studies in severe, but stable, diabetic children. In these experiments, isocalorie diets were fed with the substitution of either fructose or sucrose for glucose to the extent of 25 per cent of the total calories. Insulin requirements for good regulation were found quite the same, regardless of diet (Fig. 13). Apparently in such circumstances equal amounts of free glucose are

formed at some stage of metabolism, requiring equal amounts of insulin for re-phosphorylation and utilization.

When parenterally administered glucose leads to hyperinsulinism and hypoglucemia, there may be some advantage in substituting fructose for glucose to avoid overstimulation of insulin secretion.

AREA 4. GLYCOGENESIS AND GLYCOGENOLYSIS (FIG. 2)

In an earlier slide describing the glucokinase reaction, glycogen was shown to result from glucose-1-PO_4 as a result of the action of the enzyme phosphorylase. Recent work indicates that two other enzymes are necessary for normal formation and degradation of the glycogen molecule and that the latter has a treelike configuration (Fig. 14), with phosphorylase governing synthesis and breakdown of the straight chains of C_1—C_4 glucosidal linkages, and Amylo (1, 4 → 1, 6 transglucosidase) (branching enzyme) and Amylo 1, 6 glucosidase (debranching enzyme) with the formation and destruction of branches where there are C_1—C_6 linkages.

In normal animals, high blood sugar levels and insulin in the presence of low tissue glycogen content stimulate glycogen deposition, while hypoglycemia, strenuous exercise, and adrenaline stimulate glycogenolysis. Experimentally in the intact animal or liver slice the hormone of the alpha cell, glucagon, acts much like adrenaline. Under abnormal circumstances, anoxia and many substances poisonous to the tissues, especially liver, stimulate glycogenolysis and depress glycogenesis.

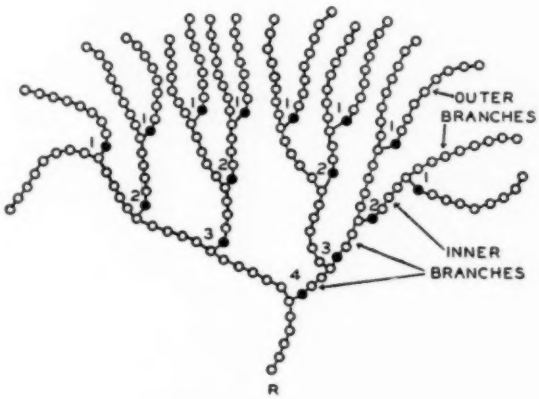

Fig. 14.

So far, in most cases of generalized glycogen storage disease (muscle involvement as well as liver and kidney) the Coris have found reduction of the debranching enzyme and an abnormal glycogen in respect to the ratio of the number of branches to the total number of glucose molecules; i.e., phosphorylase activity, being quite normal, was able to break down the outer tier of straight glucose chains but could not attack the interior ones because of the persistence of the outer set of branches

which are destroyed only by the enzyme which was absent or deficient. On the other hand, in the most severe forms of the liver-kidney variety (with normal muscle), they found qualitatively normal glycogen but absent or very deficient glucose-6-phosphatase in the liver and kidney. This enzyme normally is not present in muscle. In milder examples of this type, as was the case in the little girl shown in Fig. 15, some phosphatase was present, but less than normal. In one instance, an abnormal type of glycogen, resembling plant amylopectin with very long straight chains, was found, suggesting deficiency of the branching enzyme. Some cases were unexplained in that glycogen qualitatively was normal but much increased in amounts and neither phosphatase nor the debrancher found deficient. The findings in four cases of glycogen storage disease studied in the St. Louis Children's Hospital with tissue analyzed by biopsy or autopsy by the Coris are summarized in Table VIII.

Fig. 15.

AREA 5
(FIG. 2)

In this area is located the reappearance of free glucose, regardless of its original source. A less than normal rate of formation of free glucose would characterize most endogenous causes of *hypoglycemia,* there also being the possibility of a subnormal rate of entrance into the blood of exogenous glucose or an increased rate of utilization as additional causes of hypoglycemia. For a while gluconeogenesis from endogenous sources may be sufficient for maintenance of normal blood sugar levels despite deficient or absent intake of carboh-

TABLE VIII. FINDINGS IN GLYCOGEN STORAGE DISEASE

NAME	AGE (MO.)	STRUCTURE		GLYCOGEN				ENZYME CONTENT
					MUSCLE			
		NORMAL	ABNORMAL	LIVER %	HEART %	SKELETAL %	KIDNEY %	
Paul S.	12	+		10.0	±	±	Not determined	Glucose-6-phosphatase 1/30-150 normal
Susan S.	42	+		12.8	Normal	Normal	Not determined	Glucose-6-phosphatase slightly deficient
Deborah L.	13		+	14.2	4.7	3.5-5.1	0.1	Glucose-6-phosphatase normal Debrancher 1/10 normal
Ronald Y.	3	+		7.0	7.9		1.2	Glucose-6-phosphatase normal Debrancher: Sl low(?

drate. The integration of protein and carbohydrate metabolism is illustrated by the diagram of West and Todd (Fig. 16). Normal function of the brain is as much dependent on an adequate blood sugar level as it is on an mid-brain and medulla. For that reason the young infant usually fails to show clinical symptoms until the blood sugar reaches nearly zero values. Glucose seems much more readily utilizable by the brain than

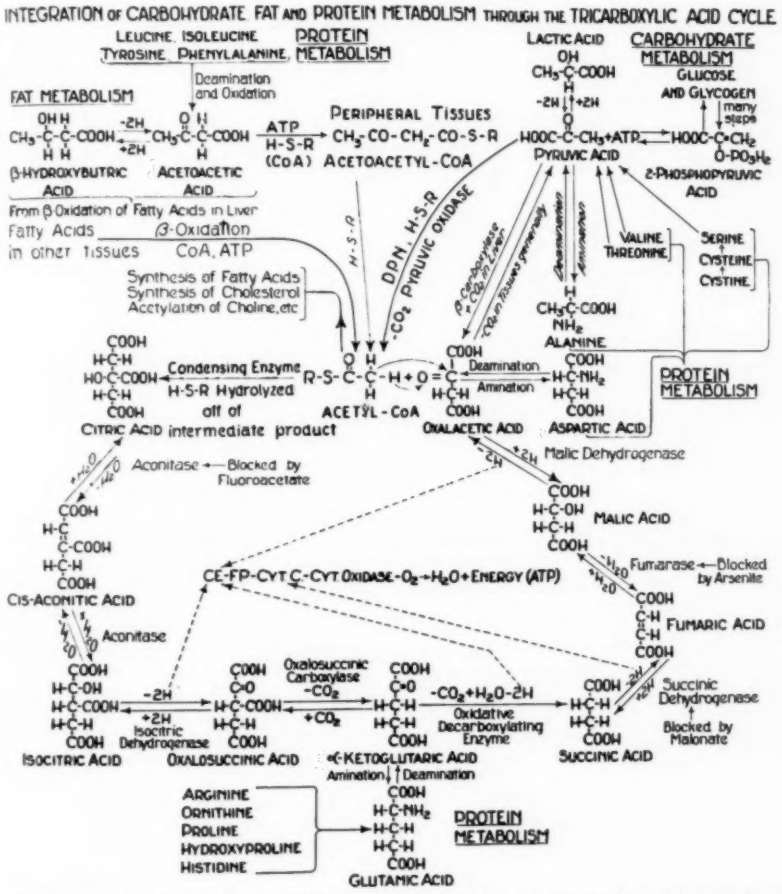

Fig. 16.—(From West and Todd: Textbook on Biochemistry. By permission of The Macmillan Co.)

adequate oxygen supply. Levels below 50 mg. per 100 ml. true sugar are considered hypoglycemic, and, in general, the lower the level the more severe the symptoms. The higher centers of the brain, however, are more sensitive to hypoglycemia than are galactose, and, as has already been mentioned, severe symptoms of cerebral failure are possible in the presence of hypergalactosemia. The duration of hypoglucemia seems also to influence not only the appearance and severity of symptoms, but also their

disappearance after glucose administration; i.e., severe symptoms may not appear immediately when the blood sugar drops to zero or near-zero levels, but, on the other hand if such low levels have been permitted to exist for several hours or longer, and severe symptoms such as unconsciousness and convulsions have developed, glucose administration, adequate for restoration of normal blood sugar levels, may not lead to their *immediate* disappearance.

The following comprehensive physiologic classification into which all of our cases of hypoglycemia could be fitted was developed some years ago.

I. True hyperinsulinism (insulin excess):
  A. Hyperactivity of islands of Langerhans:
    1. Physiologic hyperactivity (induced by excessive carbohydrate intake)
    2. Hypertrophy or hyperplasia (compensatory or pathologic)
    3. Tumor
  B. Insulin administration
II. Relative hyperinsulinism:
  A. Lack of dextrose precursor substances:
    1. Diminished absorpion from gastrointestinal tract:
      a. Starvation
      b. Loss because of vomiting, diarrhea, or fistula, with and without infection (combination of diminished food intake and increased metabolism)
    2. Liver abnormalities (decrease in glycogen stores or mobilization
  B. Lack of development or breakdown of regulatory mechanism:
    1. Normal newborn or premature infant
    2. Endocrine imbalance: adrenal or pituitary insufficiency
    3. Intracranial injury
    4. Moribund state

A simpler clinical classification follows:

I. Neonatal
II. Following intensive CHO administration
III. Spontaneous but intermittent
IV. Persistent

We will only consider neonatal hypoglycemia, which may be classified as follows:

1. Insulin sensitivity plus physiologic hyperinsulinism
2. Pathologic hyperinsulinism due to islet cell hyperplasia and hypertrophy
3. Pathologic adrenal insufficiency
4. Intracranial lesions

Insulin Sensitivity and Transient Physiologic Hyperinsulinism

Our present concept of the cause of the frequent development of hypoglycemia a *few hours* after birth in babies born of either normal or diabetic mothers is as follows:

During labor, maternal hyperglycemia is shared by the fetus and stimulates fetal insulin secretion. With the abrupt separation of the placenta, the fetus, now the newborn, finds itself suddenly cut off from an exogenous source of glucose and in a state both of hyperinsulinism, the result of previous hyperglycemia, and insulin hypersensitivity due to lack of one or more insulin antagonists—a state which seems to characterize all newborn infants, full term and premature alike. The result is a sharp fall in blood sugar for the first few hours after birth. If the fall is not extensive or persistent, clinical symptoms of hypoglycemia may not be noted. If zero or near-zero blood sugar values develop and especially if they are allowed to persist, such clinical signs as pallor, sweating, subnormal temperature, listlessness, cyanosis, twitchings, and convulsions are to be expected. Following parenteral administration of glucose and institution of regular feedings of milk and

added carbohydrates, such infants rapidly acquire a normal blood sugar regulation.

Such a concept as the above is based on the following data which have been gathered over a number of years.

Situation at Birth.—When whole blood samples (Fig. 17) are obtained as nearly simultaneously as possible from (1) the mother's capillaries or veins, (2) the infant's umbilical vein, (3) an umbilical artery, (4) strippings of the umbilical cord (mixed arterial and venous blood), and (5) the infant's heel capillaries, and true sugar determined by the Somogyi modification of the Shaffer-Hartmann method, using the sensitive low-blank reagent, the mother's sugar is always highest, and then decreasing values are noted as the blood enters the fetus and circulates back into the placenta or through the lower extremities. Absolute values vary considerably, and on one occasion hypoglycemia was already present at birth in all samples. (Diabetic mother receiving too much insulin.) Recent study has demonstrated that all the blood sugar at birth and for a number of days subsequently is glucose, lactose ingestion not being sufficient to lead to significant galactosemia.

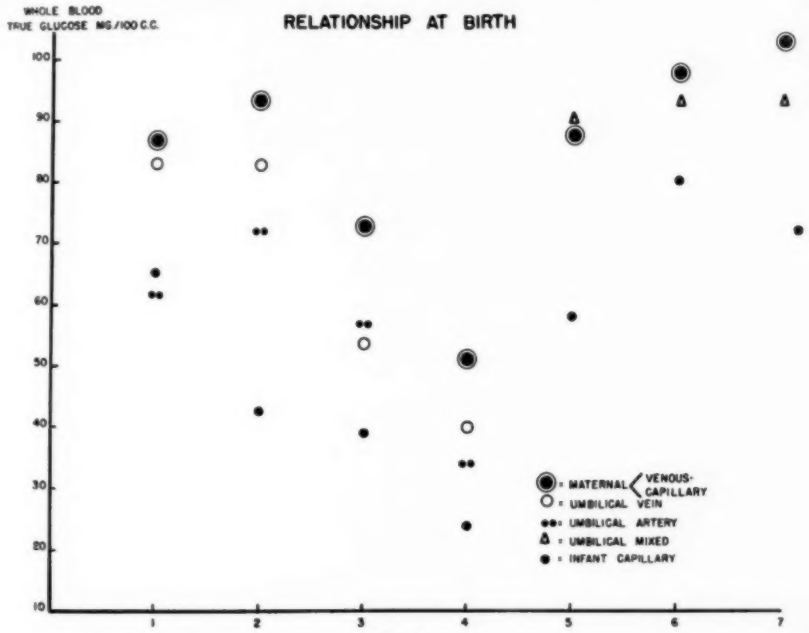

Fig. 17.

Behavior of Blood Sugar Immediately After Birth

Blood sugars obtained hourly after birth tend to fall for three to four hours, and then may rise spontaneously (Fig. 18). The lowest values of true sugar in normal infants born of normal mothers may occasionally be as low as 30 mg. per 100 ml. In infants born of diabetic mothers, zero

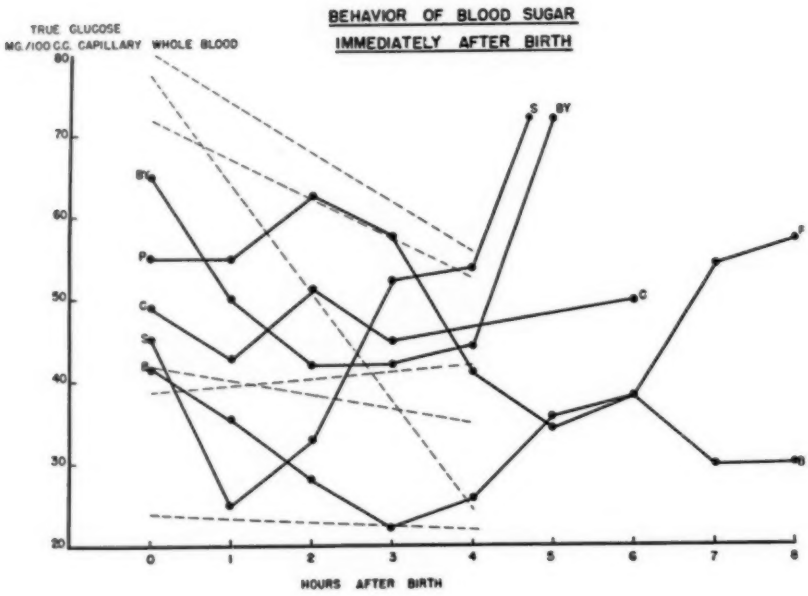
BEHAVIOR OF BLOOD SUGAR
IMMEDIATELY AFTER BIRTH
TRUE GLUCOSE
MG./100 C.C. CAPILLARY WHOLE BLOOD
80
70
60
50
40
30
20
0
1
2
3
4
5
6
7
8
HOURS AFTER BIRTH

Fig. 18.

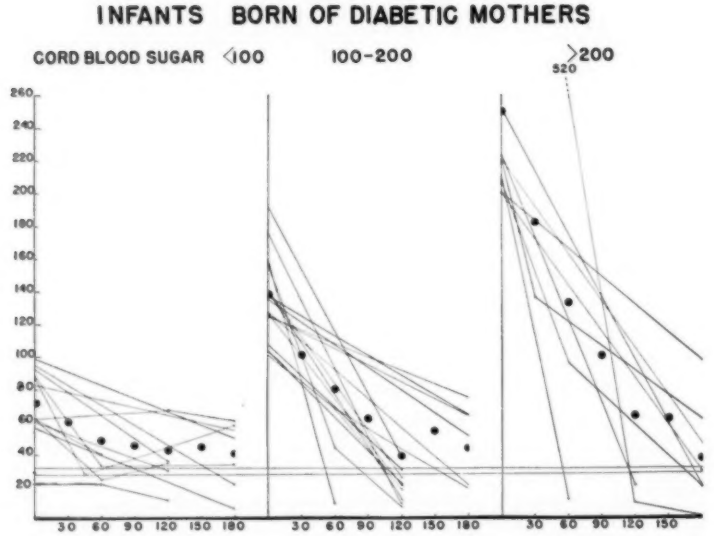
INFANTS BORN OF DIABETIC MOTHERS
CORD BLOOD SUGAR <100
100-200
>200
520
260
240
220
200
180
160
140
120
100
80
60
40
20
30 60 90 120 150 180
30 60 90 120 150 180
30 60 90 120 150

Fig. 19.

or near-zero values may result as already noted. Further observations of infants born of diabetic mothers have confirmed our earlier findings and are summarized in Fig. 19.

Blood Sugar Values After the First Day

In full-term infants born of normal mothers and fed only at the breast, hypoglycemic values continue to be noted for about five days (Fig. 20), while in full-term infants born of diabetic mothers and fed artificially soon after birth, the postnatal hypoglycemia, while often more severe, tends to be shorter and averages about three days (Fig. 21). Premature infants born of nondiabetic mothers behave similarly to full-term infants during the first five days in regard to the over-all range of values. Hypoglycemic values may continue to be seen in the second and third weeks of life, but higher values are also encountered. As a result the average

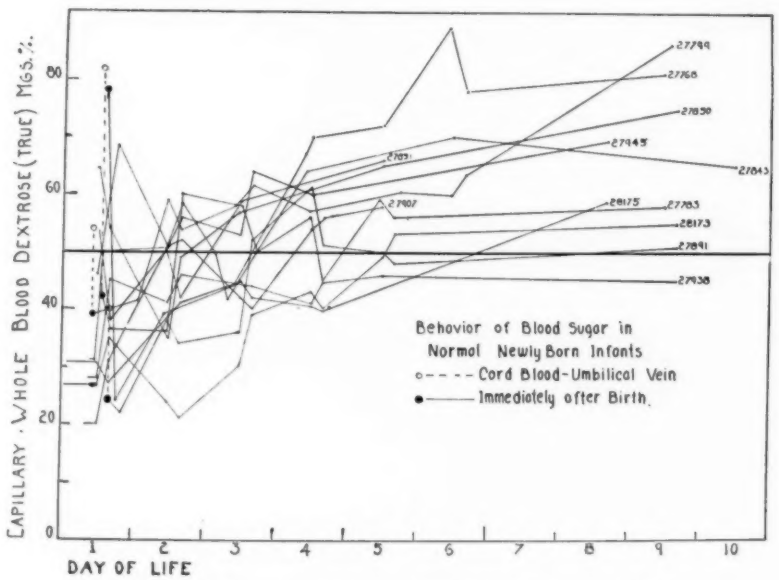

Fig. 20.—(From Hartmann and Jaudon: J. PEDIAT., 1937.)

TABLE IX. RELATION OF AGE OF PREMATURE INFANTS TO RANDOM BLOOD SUGAR VALUES

AGE (DAYS)	NO. OF DETERMINATIONS	RANGE OF VALUES MG./100 ML.	AVERAGE MG./100 ML.
1-4	19	30-78	57
	10*	32-78*	54*
5-9	9	48-82	60
10-14	20	30-104	67
15-26	32	30-104	67

*Full-term infants.

value seems to rise steadily to a plateau which is reached at age 10 to 14 days (Table IX). This plateau coincides with the attainment of a weight of 1,500 to 1,999 grams.

Response to Adrenalin.—When the blood sugar is at approximately its lowest value a few hours after birth, epinephrine administered intramuscu-

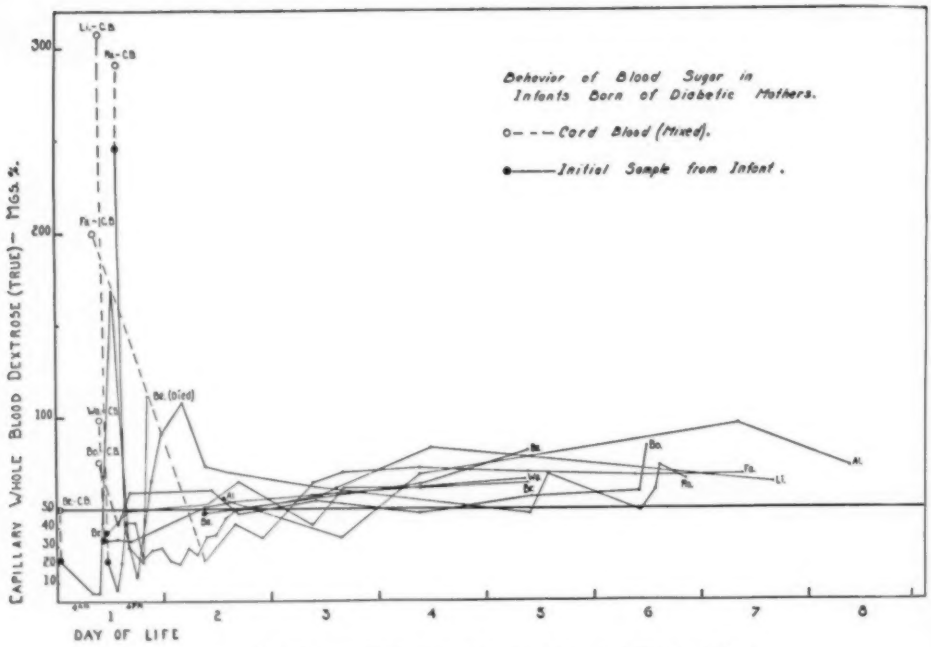
Behavior of Blood Sugar in Infants Born of Diabetic Mothers.
o- - - Cord Blood (Mixed).
●——— Initial Sample from Infant.
CAPILLARY WHOLE BLOOD DEXTROSE (TRUE) — MGS. %.
DAY OF LIFE

Fig. 21.—(From Hartmann and Jaudon: J. PEDIAT., 1937.)

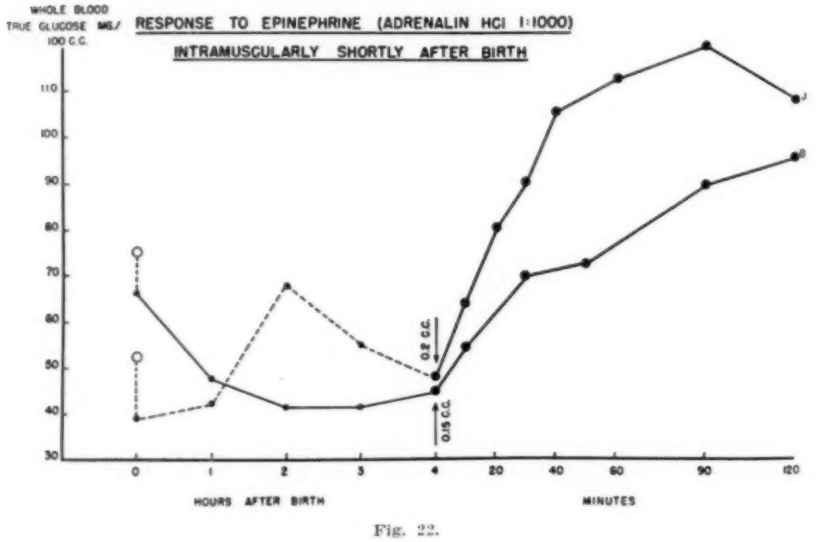

Fig. 22.

larly in liberal amount (0.2 to 0.3 ml. 1:1,000 Adrenalin) causes good blood sugar increase (Fig. 22). Such epinephrine response suggests good glycogen stores in the liver capable of being converted to glucose, and also suggests disappearance of hyperinsulinism by the fifth hour after birth.

Response to Insulin.—When 0.25 unit per kilogram of regular insulin is administered subcutaneously to infants 8 hours old, the subsequent fall of blood sugar is greater and more diminishes. The response to insulin may be almost normal in the second week. Premature infants seem to take longer in developing normal insulin resistance.

The insulin sensitivity of young infants is all the more remarkable when one considers that in the older child the test is performed after a twelve- to fifteen-hour fast, while in the young infant receiving feedings every three to four hours, it is performed no longer than such an interval after the last feeding. It has been our experience that insulin tolerance tests performed after the second meal of the day in older children with recurring attacks of hypoglycemia often do not so clearly reveal sensitivity.

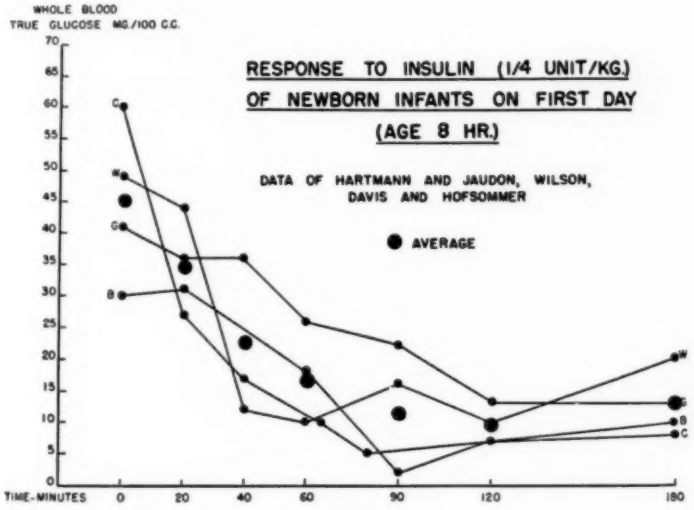

Fig. 23.

lasting (Fig. 23) than that seen in normal older children and resembles much the response of children with recurrent attacks of hypoglycemia described previously as lacking development of a good blood sugar regulatory mechanism because of adrenal or pituitary insufficiency (Fig. 24). Similar insulin tolerance tests performed in slightly older infants (Fig. 25) suggest that insulin sensitivity noted on the first day of life quickly

When epinephrine was administered during the hypoglycemic phase three hours after insulin injection, very little glycemic response was noted in a one-day (Fig. 26) and a 5-day-old infant, but normal responses were

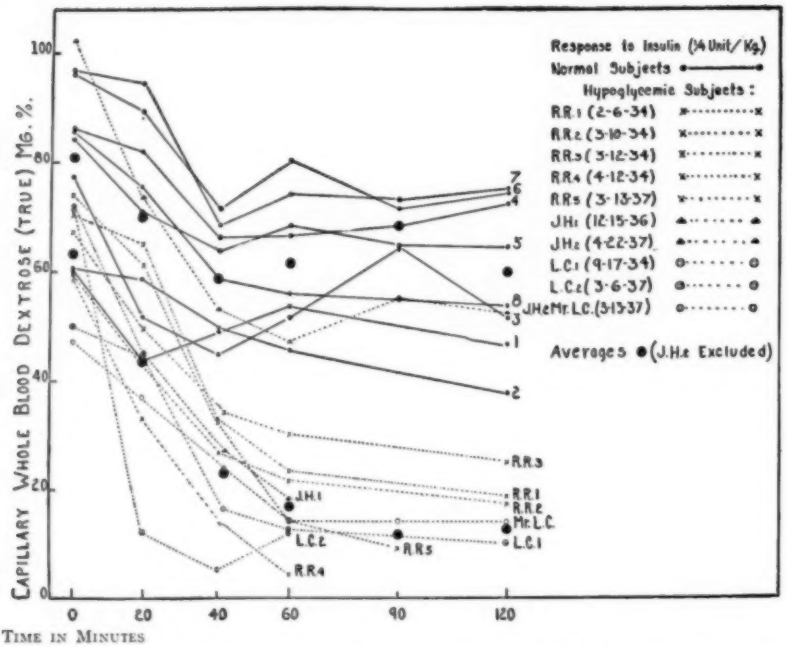

Fig. 24.—Comparison of responses to insulin of normal children and those with recurrent hypoglycemia. (From Hartmann and Jaudon: J. PEDIAT., 1937.)

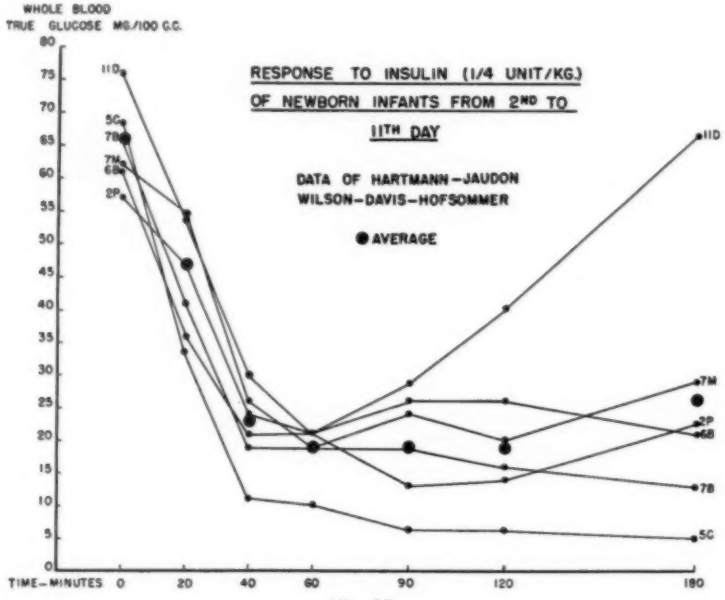

Fig. 25.

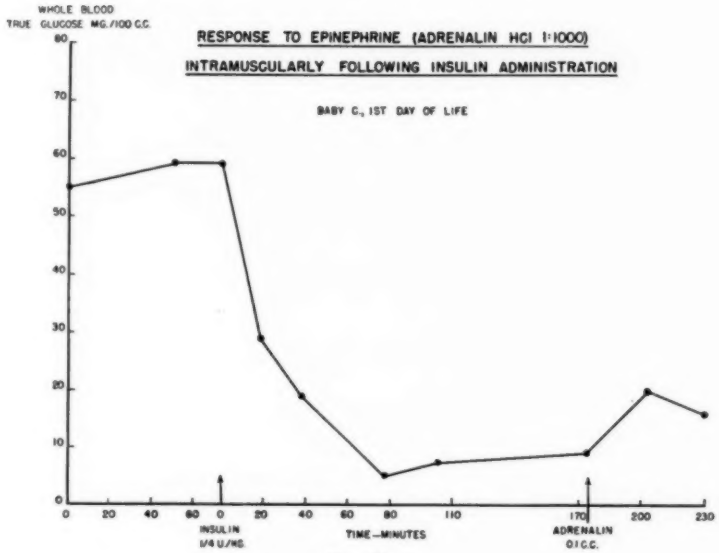
WHOLE BLOOD
TRUE GLUCOSE MG./100 C.C.
RESPONSE TO EPINEPHRINE (ADRENALIN HCl 1:1000)
INTRAMUSCULARLY FOLLOWING INSULIN ADMINISTRATION
BABY C., 1ST DAY OF LIFE
80
70
60
50
40
30
20
10
0
0 20 40 60 0 20 40 60 80 110 170 200 230
INSULIN
1/4 U./KG.
TIME—MINUTES
ADRENALIN
0.1 C.C.

Fig. 26.

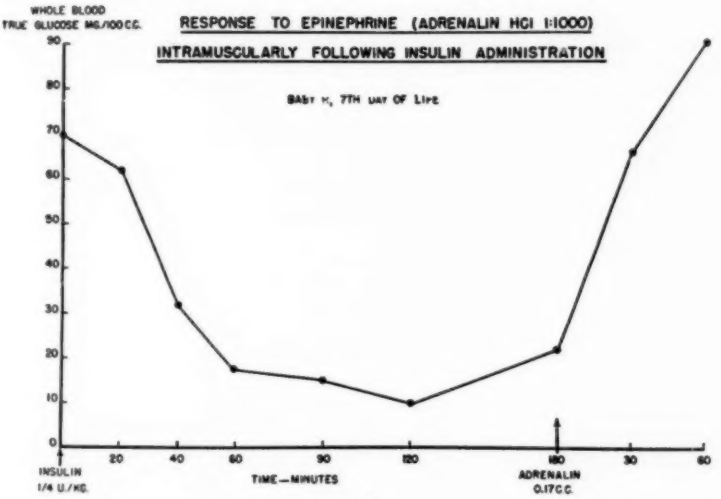
WHOLE BLOOD
TRUE GLUCOSE MG./100 C.C.
RESPONSE TO EPINEPHRINE (ADRENALIN HCl 1:1000)
INTRAMUSCULARLY FOLLOWING INSULIN ADMINISTRATION
BABY H., 7TH DAY OF LIFE
90
80
70
60
50
40
30
20
10
0
20 40 60 90 120 180 30 60
INSULIN
1/4 U./KG.
TIME—MINUTES
ADRENALIN
0.17 C.C.

Fig. 27.

seen in a 3-day- and a 7-day-old (Fig. 27) infant. Such lack of insulin antagonism by epinephrine also characterizes the insulin-sensitive children with recurrent hypoglycemia described previously (Fig. 28). Could it be that the latter represent children slow to outgrow a condition normally present at birth?

Pathologic Islet Cell Hyperplasia and Hypertrophy

In an earlier study published in 1937, two cases of fatal islet cell hyperplasia and hypertrophy were described, one born of a diabetic (Fig. 29) and the other a nondiabetic mother (Fig. 30).

Since then four more cases have been encountered where neonatal hypoglycemia was noted and death occurred, and where autopsy findings revealed pathologic hypertrophy and apparent increase in number of the islet cells, in only one instance was the mother diabetic. It is clear, therefore, that diabetes in the mother is not a prerequisite for the development of pathologic degrees of islet cell hypertrophy. The method of fixation of the tissue blocks, unfortunately, was such as not to allow recutting of sections and staining differentially for alpha and beta cells.

In all six of these cases hypoglycemia and death occurred sometime during the first four days of life, and, until a few years ago, I felt that pathologic hypertrophy and hyperplasia were incompatible with life beyond the early neonatal period. In a personal communication, however, C. Van Beek of Leiden, Holland, described a child, who after exhibiting severe hypoglycemic symptoms during the first week of life, then did well, only to die

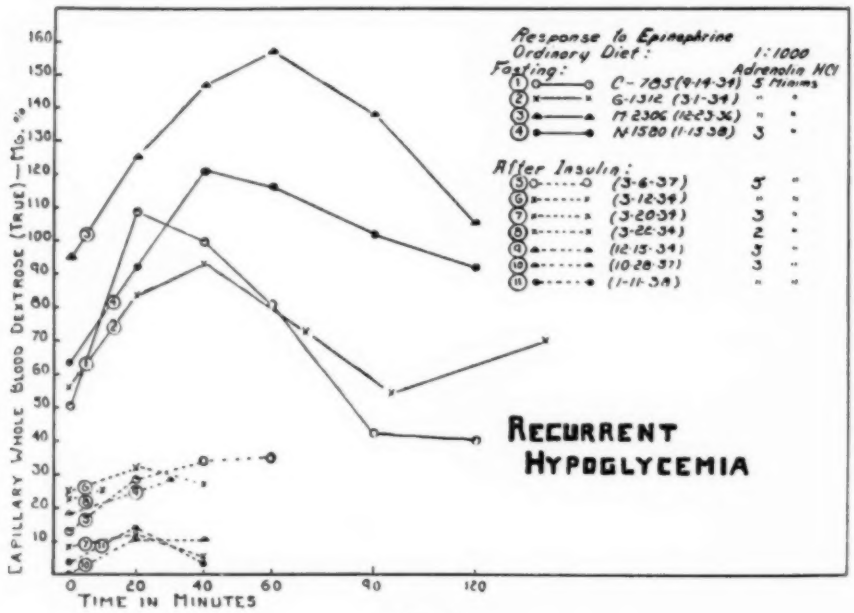

Fig. 28.

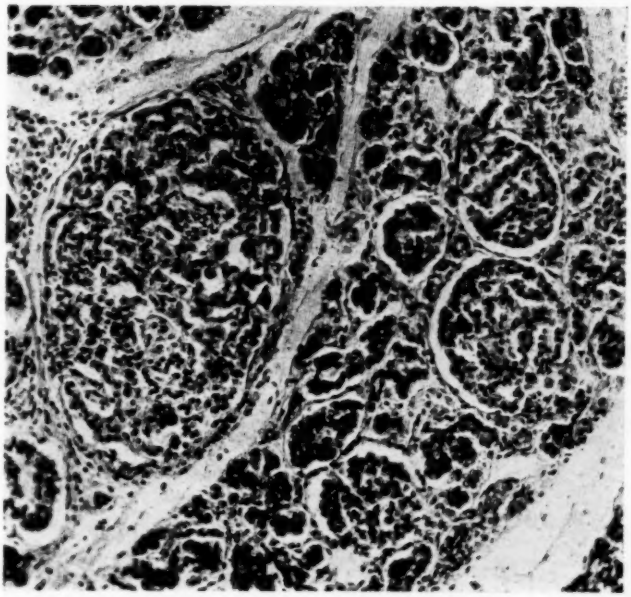

Fig. 29.—(From Hartmann and Jaudon: J. PEDIAT., 1937.)

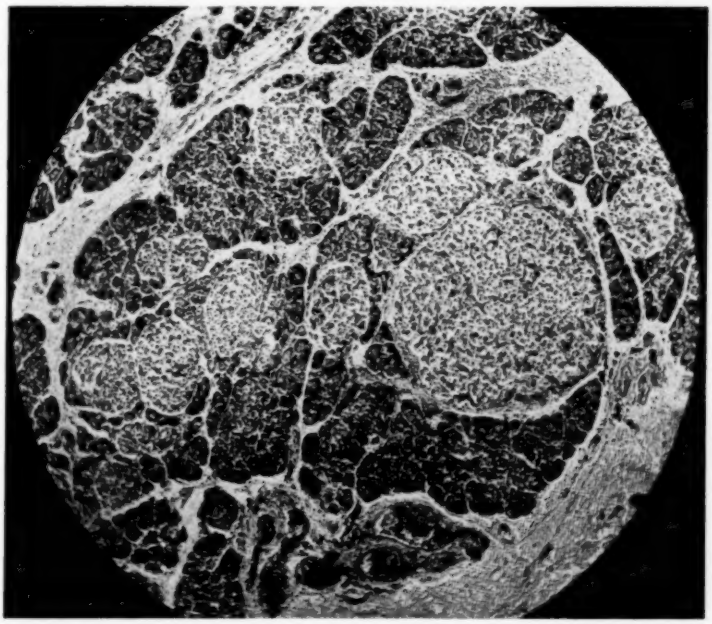

Fig. 30.—(From Hartmann and Jaudon: J. PEDIAT., 1937.)

of meningococcal infection at the age of 5 months. At autopsy there was found marked pathologic hypertrophy of the islet cells. In some way good blood sugar regulation must have developed despite the apparent pathologic hyperinsulinism. As with our cases, however, differential staining for alpha and beta cells was not done.

So far as I am aware, no insulin-secreting adenoma has been found in a newborn infant, the youngest case on record being that of a 6-month-old child reported by Rabinowitch, where death occurred during hypoglycemia and where a microscopic-sized adenoma was found at autopsy.

Pathologic Adrenal Insufficiency

In our 1937 study on hypoglycemia, a newborn infant was described who died on the third day of life with a zero blood sugar, and in whom autopsy showed only massive hemorrhagic destruction of the adrenals to account for the extreme hypoglycemia. Since then several more similar cases have been noted. In such cases, hypoglycemia, of course, is only one result of total adrenal failure. It is interesting that at first it seems the most important aspect of adrenal failure, in that glucose administration is at first dramatic, but later fails to improve the child.

Intracranial Causes

In the previous study on hypoglycemia already twice alluded to, mention was made of six cases of hypoglycemia associated with intracranial abnormalities. Since then, other cases have been encountered where an intracranial lesion seemed to be the main causative factor of the associated hypoglycemia. Most of them represented complicated situations, however, so that the exact role played by the intracranial lesion in producing hypoglycemia could not easily be evaluated.

AREA 6. LACTATE METABOLISM (FIG. 2)

Under ordinary conditions of health and activity, lactic acid is present in the blood and extracellular fluid in the concentration of 1 to 2 meq. per liter. While small amounts may be contributed directly by food, i.e., lactic acid milk, most of it results from the anaerobic glycolysis of glucose or glycogen. Its rate of utilization matches the rate of formation and little escapes into the urine. When its rate of formation is unusually rapid, such as occurs in severe exercise where ATP is used up faster than oxidative processes can form it, accumulation of lactic acid in the muscle occurs and is followed by its more rapid diffusion into the blood where it may reach concentrations ten or more times the normal, with resulting lactic acid acidosis. Under such conditions there is increased excretion into the urine, but much of the lactate circulating in the blood can be saved and utilized by the liver.

Just one step, the loss of two hydrogens effected by lactic dehydrogenase is required for lactate to be oxidized to pyruvate and thus enter the carbohydrate cycle near its center, with the possibility of being metab-

TABLE X. STUDIES IN FASTING PHLORHIZINIZED CATS*

	β $C^{14}H_3$	α $C^{14}HOH$	COOH
28.2%	C^{14}	in urinary glucose in 24 hours	
7.3%	C^{14}	in liver fat in 24 hours	
22.4%	C^{14}	in muscle fat in 24 hours	
10.2%	C^{14}	in ketone bodies in 24 hours	
17.3%	C^{14}	in respiratory CO_2 in 4 hours	

*From Gurin, Delluva, and Wilson: J. Biol. Chem., 1947.

olized along four different pathways. In isotopic experiments with labeled lactate administered to fasting phlorizinized cats, Gurin and his co-workers (Table X) demonstrated that all four possible pathways were taken simultaneously. Later, Chaikoff and

TABLE XI. STUDY OF NORMAL RAT LIVER, DIABETIC LIVER, AND INSULIN-TREATED DIABETIC LIVER*

β $C^{*}H_3$ (3)	α $C^{*}HOH$ (2)	$C^{*}OOH$ (1)

2% of α and β carbons → fatty acids in normal livers.

30-60% of carboxyl carbon → CO_2 in all 3 states $\left(\frac{\alpha C}{\beta C} = \frac{2}{1}\right)$.

About 100-fold increase of α and β carbons → fatty acids in insulin-treated diabetic livers compared to untreated animals. Also less CO_2.

Conclusion: Insulin shifts reaction from oxidation to synthesis.

*From Felts, Chaikoff, and Osborn: J. Biol. Chem., 1951.

Elevation of blood lactate, significant in the production of acidosis, is seen clinically, mainly when circulation fails because of extreme hemoconcentration or cardiac failure, or when convulsions are severe and continuous and attended by cyanosis. In the anhydremic subjects, blood lactic acid returns to normal almost immediately after hydration, and in the children with convulsions, just as rapidly after convulsions cease. In children with protracted cardiac failure, not only may lactic acid metabolism continue to fail with persistent elevation of its concentration in the blood, aggravating the carbonic acid type of acidosis already present, but, as a result of its continued nonutilization, severe and persistent hypoglycemia may develop. As a result of the renewal of interest in blood sugar during the last two years which our galactose observations stimulated, we encountered several cases of cardiac failure with significant hypoglycemia, two of which are shown in Table XII. Just how much the hypoglycemia

TABLE XII. HYPOGLYCEMIA DURING CARDIAC FAILURE

DATE	TIME	MG. PER 100 ML. TOTAL	MG. PER 100 ML. GLUCOSE	MG. PER 100 ML. GALACTOSE	MEQ./L. CO_2 CONTENT	% O_2 SAT.	REMARKS
12/12/53		36					Case Sheila T., aged 6 mo. Potts-Smith operation 12/14/53. Cyanosis, dyspnea, hypothermia preoperative and for 1 week postoperative. Parenteral glucose required. Recovered.
12/17/53		89					
12/21/53	4:00 A.M.	10					
	10:50 A.M.		8	0			
	9:30 P.M.	34			11.2		
12/22/53		89					
12/31/53						64	
10/ 5/54						26	Case Darrell C., aged 4 mo. Transposition of great vessels plus ventricular septal defect. Parenteral glucose required. Patient died 10/29/54.
10/ 7/54		18					
10/ 9/54			10	19			
10/13/54			28	0		43	
10/14/54			14	14			
10/16/54			19	8			
10/21/54			27	0			
10/28/54					13.2		

his associates, also with labeled lactate, demonstrated that insulin favored the conversion of active acetate (acetyl coenzyme A) into fatty acid as contrasted to its oxidation to CO_2 in the Krebs tricarboxylic acid cycle (Table XI).

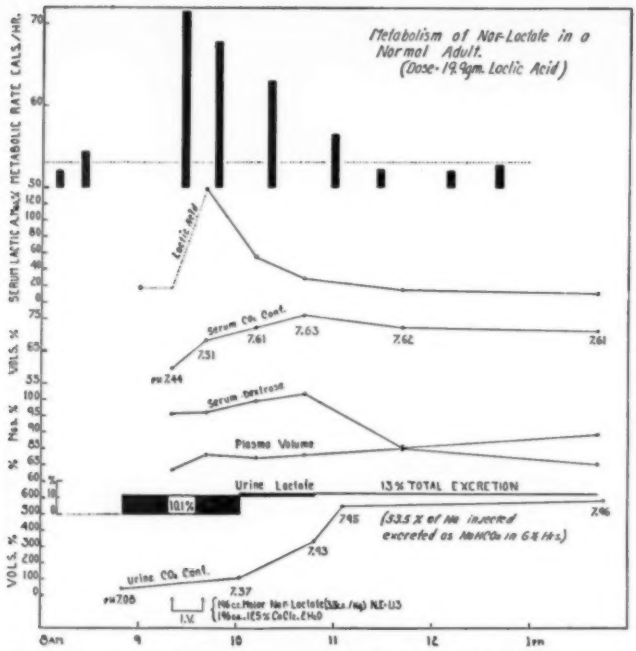

Fig. 31.—(From Hartmann, Perley, Basman, Nelson, Asher, and Morton: J. PEDIAT., 1938.)

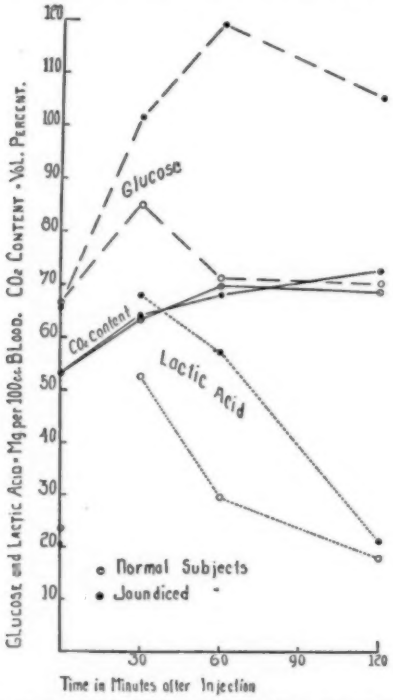

Fig. 32.—Comparison of responses of normal subjects and subjects with acute hepatitis to the intravenous injection of sodium r-lactate. (From Hartmann and Senn: J. Clin. Invest., 1932.)

contributed to the cardiac failure is not clear, but certainly it must have been an added handicap.

In our many observations of the effects of administration of a racemic mixture of Na-lactate to acidotic infants and children during the past twenty-five years, we have been impressed with the fact that nothing short of severe anoxia interferes appreciably with lactate metabolism, the appearance of bicarbonate (Fig. 32). In much more severe types of liver damage, the delay may be a little longer (Fig. 33).

Occasionally it has been stated in the literature that Na-lactate is ineffectual in the treatment of acidosis in premature infants. We have not found that to be true. It is true, however, that larger doses than usual

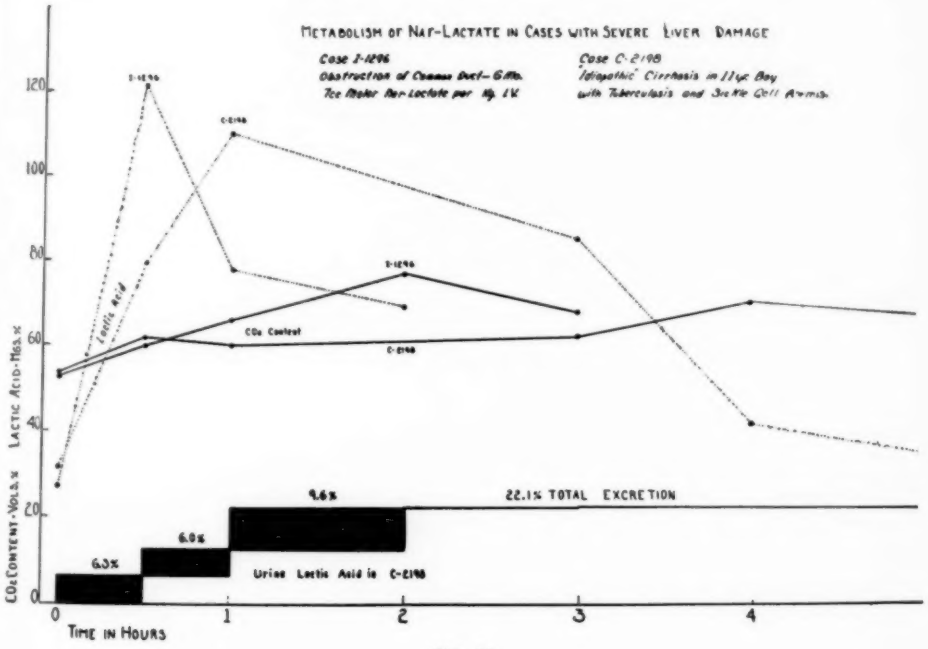

Fig. 33.

natural isomer being handled more effectively than the Na-d (−) lactate, the latter often escaping in the urine in appreciable amounts whenever diuresis follows immediately upon its intravenous administration (Fig. 31).

In the degree of liver damage such as may be associated with acute infectious hepatitis, there is approximately only an hour's delay in the disappearance of injected lactate and may be needed, as demonstrated by some of our earliest studies. I have always felt that in such cases, the reduction in $BHCO_3$ was also accompanied by severe reduction in pH, and that as the latter recovered during therapy, protein and phosphate buffers claimed fixed base which otherwise might have restored $BHCO_3$ more rapidly, just as occurs in diabetic acidosis (Figs. 34 and 35).

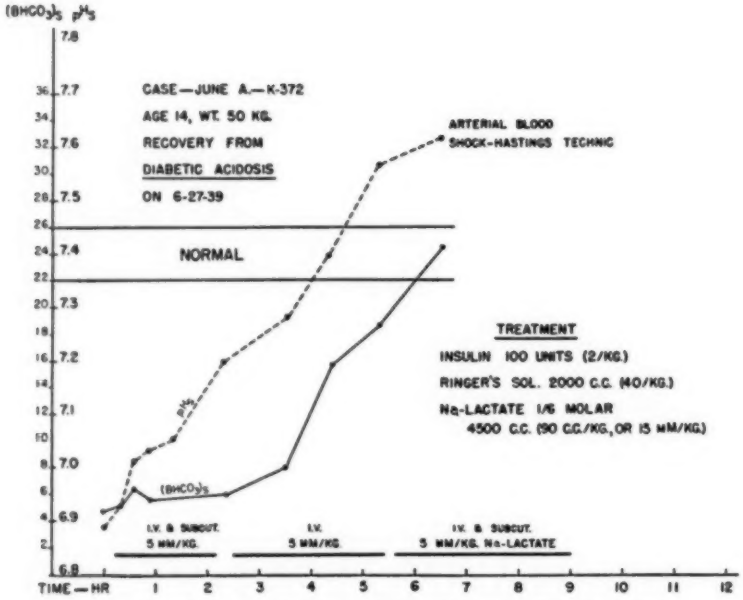

Fig. 34.—(From Hartmann and Erganian: J. PEDIAT., 1947.)

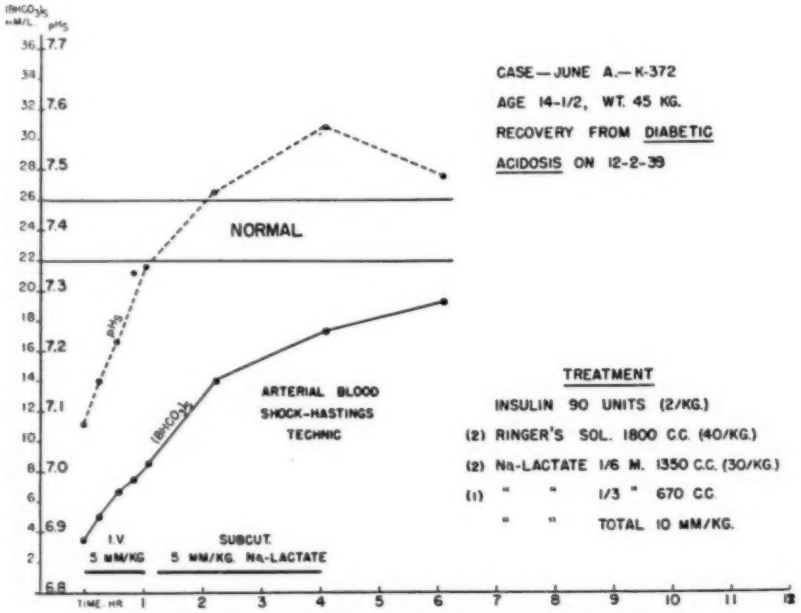

Fig. 35.—(From Hartmann and Erganian: J. PEDIAT., 1947.)

It has also been stated in the literature that the acidosis of glycogen storage disease is unaffected by Na-lactate therapy. In our only case of severe acidosis associated with the liver-kidney variety, Na-lactate was effectual (Fig. 36). From its position in the glucose cycle, this is what would be expected (Fig. 2).

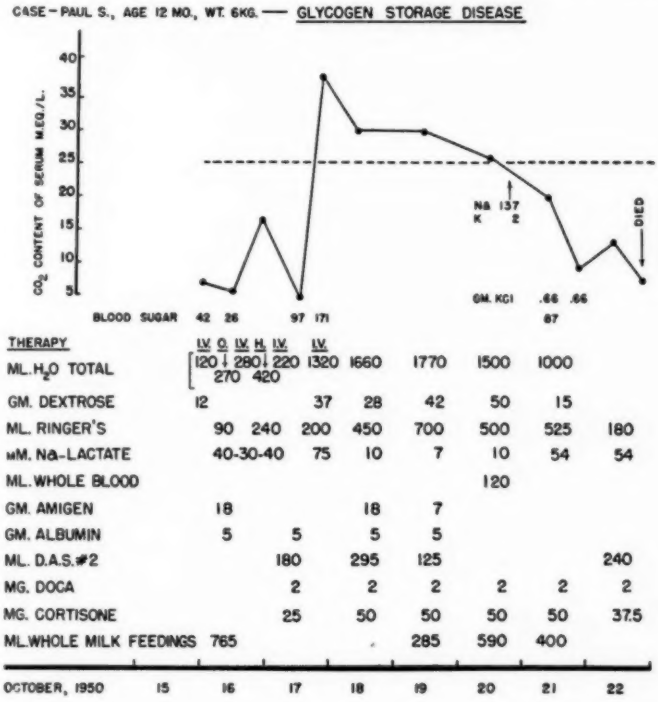
CASE – PAUL S., AGE 12 MO., WT. 6KG. — GLYCOGEN STORAGE DISEASE
CO_2 CONTENT OF SERUM M.EQ./L.
40
35
30
25
20
15
10
5
Na 137
K 2
DIED
GM. KCl .66 .66
BLOOD SUGAR 42 26 97 171 87
THERAPY IV O IV H IV IV
ML. H_2O TOTAL 120 ↓ 270 280 ↓ 420 220 1320 1660 1770 1500 1000
GM. DEXTROSE 12 37 28 42 50 15
ML. RINGER'S 90 240 200 450 700 500 525 180
mM. Na-LACTATE 40-30-40 75 10 7 10 54 54
ML. WHOLE BLOOD 120
GM. AMIGEN 18 18 7
GM. ALBUMIN 5 5 5 5
ML. D.A.S.#2 180 295 125 240
MG. DOCA 2 2 2 2 2 2
MG. CORTISONE 25 50 50 50 50 37.5
ML. WHOLE MILK FEEDINGS 765 285 590 400
OCTOBER, 1950 15 16 17 18 19 20 21 22

Fig. 36.

AREA 7. KETOSIS
(FIG. 2)

Under normal conditions, there seems always to be enough oxaloacetate coming from carbohydrate and protein precursors to react with "active acetate" which recently has been identified as acetyl coenzyme A (Fig. 37), and to send it into the Krebs cycle where it is oxidized to CO_2, thus preventing two molecules of the active acetate from condensing to form much of the four carbon aceto-acetate. The ketosis of starvation and diabetes seems readily explained by assuming a situation characterized by excessive production of acetyl coenzyme A from fatty acid and deficient formation of oxalo-acetate from carbohydrate and protein.

As a simple expression of relationships, the formula which P. A. Shaffer developed many years ago has proved to be accurate and helpful in the prescription of ketogenic diets. His formula is as follows:

$$\frac{\text{Total Metabolism (Cal./24 hr.)} - 100 \times \text{Urinary N (Gm./24 hr.)}}{50} =$$

Gm. CH_2O/24 hr. necessary to prevent ketosis.

Certainly when it is due to starvation, ketosis can be abolished very easily and quickly by administrating glucose or fructose. The amount of carbohydrate needed is such as to provide about 10 per cent of the total calories being expended. When it is due to diabetes, ketosis can usually be abolished in six to eight hours if as much as 1 unit of insulin per kilogram of body weight is administered. More insulin does not accelerate the abolition of ketosis. In the usual diabetic child in severe ketosis, the blood sugar is high enough so that only insulin administration is required to abolish ketosis. When the blood sugar is less than 300 mg. per 100 ml., additional carbohydrate administration may be necessary to permit the required amount of insulin; otherwise hypoglycemia may result before ketosis is abolished.

There are two conditions, however, in which ketosis may be more difficult to correct. One is the severe type of salicylate intoxication. Despite administration of large amounts of glucose, with or without added insulin, ketosis may persist for several days, practically as long as salicylate remains in the body. In such instances, it seems necessary to assume some defect of oxidation of acetyl coenzyme A in the extrahepatic tissues, which is independent of availability of oxalo-acetate and the rate of producion of active acetate.

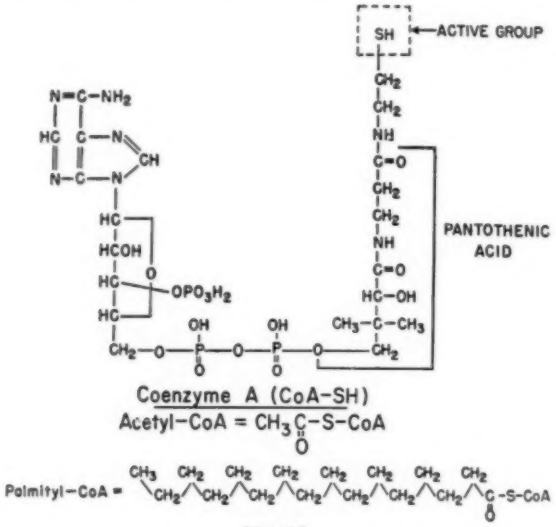

Fig. 37.

The other condition is that of snakeroot poisoning. We have encountered only one example of this condition, but it was a fascinating case. This child, a girl of 12 years, was brought in by ambulance one night to the hospital in a state similar to that of diabetic coma. She reeked of acetone and was extremely acidotic, without, however, hyperglycemia or glycosuria. As may be noted from Fig. 38, it took approx-

imately four times as long to relieve her of her ketosis and acidosis as it would have if she had been diabetic.

Her story was this: She lived in a rural area in neighboring Illinois, and was in the habit of drinking raw milk from the family cow. During several previous menstrual periods, the child had seemed unusually weak and lethargic, and during the last period, just before hospital admission, she became extremely weak and

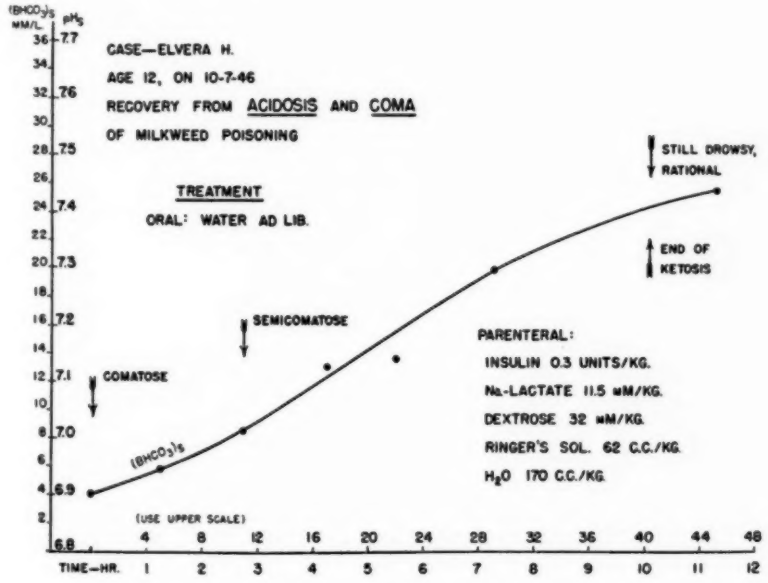

Fig. 38.

constituents, the cattle gradually become ill with the "trembles," a form of weakness due apparently to hypoglycemia. They secrete the toxic substance into the milk, and people drinking such raw milk become gradually intoxicated. Tremendous breakdown of protein with greatly increased urinary nitrogen excretion characterizes the condition. There is also often hypoglycemia, and, occasionally, as in our child, ketosis and acidosis. In lethargy gradually developed into deep coma.

As a result of work done by Harold Bulger some thirty years ago, I think we have at least a partial explanation of the condition. During drought, cattle tend to graze in the shaded woods where they will eat the snakeroot weed if present. As a result of one of its oily, heat-labile some way as yet not understood, metabolic changes associated with menstruation aggravate the condition.

AREA 8. LIPOGENESIS (FIG. 2)

As mentioned previously, Chaikoff and his associates demonstrated that in the absence of insulin, labeled precursors of acetyl-coenzyme A tended to be oxidized more in the Krebs cycle

and converted less into fat than when insulin was present. The rapid loss of fat which the untreated diabetic patient undergoes may be partially explained by this effect of insulin, as

Fig. 39.

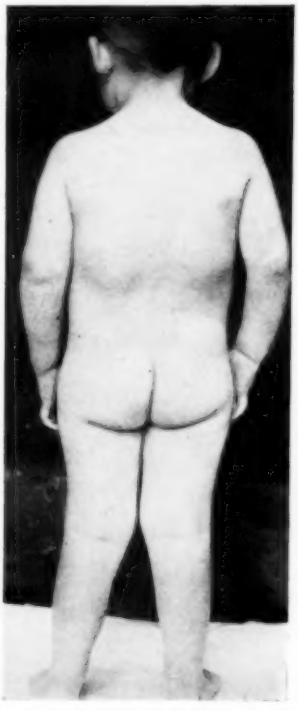

Fig. 40.

well as by the rapid production of fat which often takes place in the treated diabetic. The fat pads which develop in the areas of injection of the soluble, quick-acting regular insulin suggest that insulin under such circumstances might have a local lipogenic effect. One of our earliest diabetic patients treated with insulin in 1922 showed the local and systemic lipogenic effects of insulin in a striking fashion (Figs. 39 and 40). The newer, less soluble insulins, which are perhaps absorbed as rapidly as dissolved, have much less local effect.

COLORIMETRIC DETERMINATION OF BLOOD PLASMA pH

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IN 1915 Levy and associates[1] developed a method to detect changes in plasma hydrogen ion concentration by adding an indicator, phenol red, and visually comparing the resultant color with previously prepared standards of known pH. Cullen[2] in 1922 improved upon this method of plasma pH determination. His method was later modified by Hastings and Sendroy.[3] Still later Van Slyke and coworkers[4] developed a spectrophotometric technique for the measurement of plasma pH. The method used in our series has been modified after Van Slyke by Cohn.[5]

As shown by Rutledge,[6] the principle of all colorimetric pH determinations depends upon the color changes of an indicator, which varies when in acid or alkaline solutions. The optical density of such solutions is additive, and absorbs light of any given wave length, depending upon the depth of color. Since the color is dependent upon the hydrogen ion concentration, measurement of the wave length variation constitutes an indirect measure of the pH.

REAGENTS

The reagents needed are (a) Sorensen's phosphate buffers prepared as 0.5 molar solutions and diluted to pH 7.1, 7.4, and 7.7; (b) phenol red prepared as a stock solution and diluted to the required 40 meq. per liter solution; (c) a 22.5 per cent solution and a 0.9 per cent solution of NaCl; and (d) a 0.02 normal NaOH solution used for neutralization. Neutralized mineral oil is used to cover the blood sample when drawn and to cover the unknown saline-dye-plasma solution. These reagents are stable and may be made up and stored in the refrigerator prior to use.

GLASSWARE

For this procedure the glassware required (in addition to that used in storing the reagents) are two 50 c.c. volumetric flasks; four 5 c.c. volumetric pipettes; one 2 c.c. volumetric pipette; three 1 c.c. graduated pipettes, and as many 1 c.c. graduated pipettes as there are samples of blood to be tested. Three spectrophotometer cuvettes (80 by 135 mm.) are required, plus two cuvettes for each plasma sample to be tested.

A Beckman Junior spectrophotometer was used in this series.

PROCEDURE

An optical density curve for the spectrophotometer employed must be first determined, using a wave length of 550 millimicrons. The densities are plotted for pH values of 7.1, 7.4, and 7.7 which have been prepared using the buffer solution previously mentioned. Three determinations suffice

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since the curve is linear. Before the standard readings are taken, the solutions are warmed in a water bath and read at 38° C. A typical curve and the one used in this series is shown in Fig. 1.

Cullen[2] maintained the temperature of his solution at 20° C. and used a correction factor to convert to 38° C. Later procedures advocated controlling the temperature of the solution at 38° C. Van Slyke and associates[4] reported that 1° of temperature change altered the pH by about 0.01 pH unit. Cohn[5] stated that there may be as much as 0.8 pH unit variation in a determination when run at 25° C. as compared with 38° C. The lower the temperature the higher the pH reading.

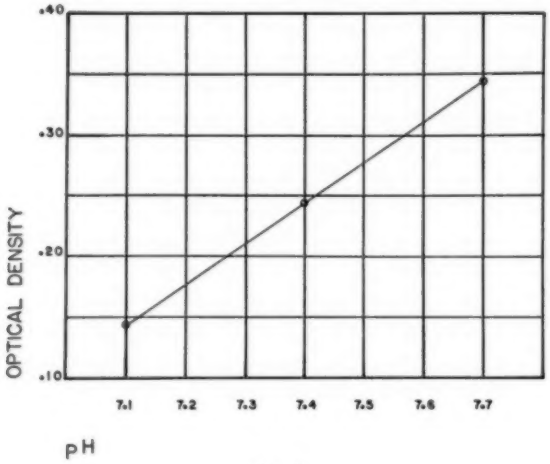

Fig. 1.

The blood should be drawn without stasis. If a tourniquet is used it should be removed before withdrawing the sample. The syringe should be dry and tight. The blood should be placed immediately into a dry test tube containing a thin film of heparin under a layer of neutralized mineral oil. The hazard and difficulty in using a syringe containing mineral oil is probably not justified. As shown by Martin and Lepper,[7] the effect of loss of carbon dioxide on the pH determination is not appreciable if the blood drawn was not exposed to the air for longer than one minute. The specimen is then centrifuged at 15,000 revolutions per minute for ten minutes. After centrifugation the blood may remain under oil for three hours without significantly effecting the pH determination.[8] Immediately prior to the determination a neutralized saline-phenol red dye solution is prepared. The pH of this solution should be between 7.4 and 7.6 pH units.[4] This may be determined visually by its faint pink color. Two-tenths cubic centimeter of the unknown plasma is then added to 5.5 c.c. of the neutralized saline dye solution in a cuvette under neutralized mineral oil. A control tube, using 5.5 c.c. of a 0.9 per cent saline solution and 0.2 c.c. of the plasma, is prepared. The spectrophotometer is then adjusted

to a zero reading at a wave length of 550 millimicrons with a water blank. The standard, control, and unknown plasma-dye solutions are heated at 38° C. for five minutes and the determinations read in the spectrophotometer immediately.

EXPERIMENTAL DATA

This is a report of 107 plasma pH determinations. Of these, thirty-four are of normal adults, thirty of banked blood, and forty-three of children who were patients either at Children's Memorial Hospital or the University of

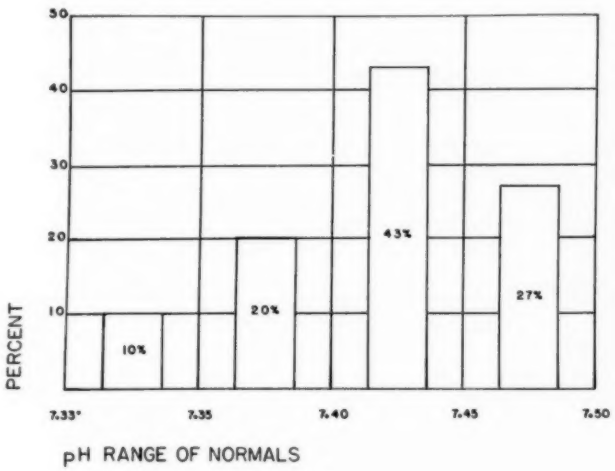

Fig. 2.

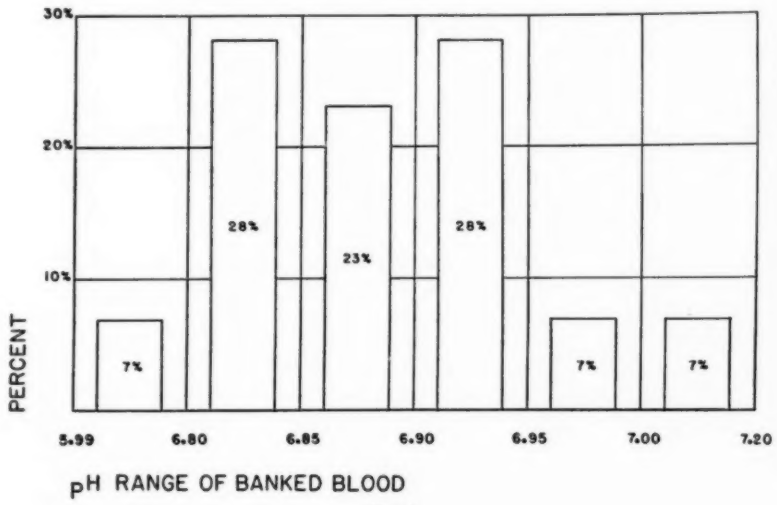

Fig. 3.

Nebraska Hospital. The normal group was used to establish a technique and to ascertain the variation and error to be expected. The hydrogen ion concentration of the plasma of the normal group varied from 7.33 to 7.50 units. The variation of this group compared favorably with that reported by Earle and Cullen[9] whose series varied from 7.33 to 7.51 pH units. Kelsey and Leinbach[8] report their range of pH variation to be from 7.30 to 7.56. Fig. 2 depicts the pH variation of our normal group.

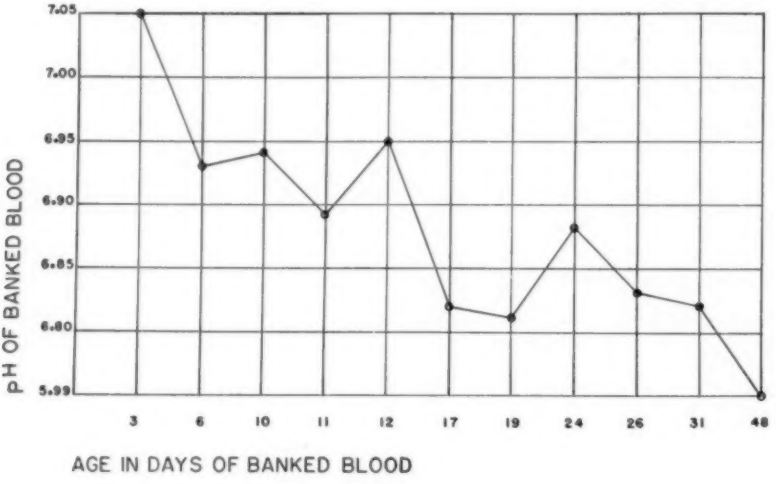

Fig. 4.

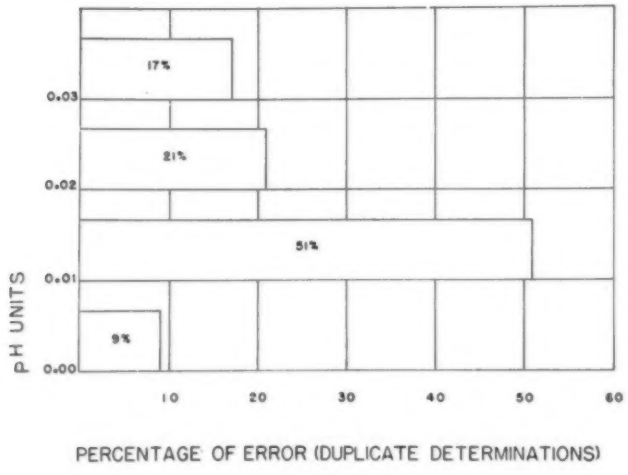

Fig. 5.

Banked blood was originally used as a volume source of readily available

blood. The pH variation was from 5.99 to 7.20 pH units. The marked acidity of this blood was striking. This suggested a possibility of unfavorable reactions when such blood is administered, particularly in quantities required for exchange transfusions. The pH range of banked blood is depicted in Fig. 3.

A correlation between the age of the banked blood and the pH was made. The curve is established with a decreasing pH with an increasing age of the blood samples as shown in Fig. 4.

It is beyond the scope of this report to include a detailed clinical summary of the pediatric patients on whom plasma pH determinations were done. The patients presented symptomatology of the following conditions: nephrosis in marked acidosis; poliomyelitis with hyperventilation in an iron lung; diabetes in acidosis; pneumonia with reduced respiratory exchange; and fibrocystic disease with marked pulmonary involvement.

ERROR

The range of error found on duplicate determinations of single specimens varied from 0.00 to 0.03 pH unit. The average error was 0.014 pH unit. This is shown in Fig. 5.

SUMMARY

A method for the determination of blood plasma pH has been presented. A typical optical density curve has been shown. A pH range of normal blood plasma has been established. The hydrogen ion concentration of banked blood and changes with age of the blood have been presented. Several clinical cases have been mentioned in which this determination was found to be of value. The range of error on duplicate determinations of single specimens has been stated.

This technique is not difficult and appears to offer a simple and reliable method in establishing diagnosis and following patients with disturbances in acid-base equilibrium.

Acknowledgment is made to Dr. John R. Schenken, professor in pathology and bacteriology, University of Nebraska, College of Medicine, and pathologist, Nebraska Methodist Hospital and Children's Memorial Hospital, Omaha; to Dr. Herbert P. Jacobi, chairman of the department of biochemistry, University of Nebraska, College of Medicine, Omaha; to Dr. Herman Jahr, chairman of the department of pediatrics, University of Nebraska, College of Medicine, Omaha; and to Dr. J. Harry Murphy, chairman of the department of pediatrics, Creighton University, College of Medicine, Omaha, for their guidance, interest, and professional support in the preparation of this paper.

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STUDIES OF 17-HYDROXYCORTICOSTEROIDS

XI. Relation of Plasma Concentrations to Urinary Excretion in Patients Treated for Rheumatic Fever

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PREVIOUS reports from this laboratory concerning studies of adrenal cortical function in children with rheumatic fever have indicated that these patients have relative adrenal cortical insufficiency.[1-3] The plasma 17-hydroxycorticosteroid (17-OHCS) concentrations and the response of these concentrations to adrenal stimulation,[4, 5] as well as urinary 17-OHCS excretion,[6] are influenced in a characteristic manner by therapy with ACTH, cortisone, or salicylates. The purpose of this report is to describe the interrelationship observed between plasma 17-OHCS concentrations and urinary 17-OHCS excretions in patients with rheumatic fever in whom various therapeutic regimens were used.

MATERIALS AND METHODS

The subjects of this study were thirty children, aged 6 to 15 years, in whom a diagnosis of active rheumatic fever was established according to the criteria of Jones,[7] with the modifications introduced by Denny and associates.[8] Serial plasma and twenty-four-hour urine samples for 17-OHCS determinations were obtained from these patients during the period of therapy as well as in the pre- and post-therapy periods. Plasma 17-OHCS was determined by the method of Nelson and co-workers[9, 10] and urinary 17-OHCS by the method of Glenn and Nelson.[11]

The forms of therapy used included cortisone* given orally, ACTH gel† given intramuscularly, and salicylate given orally. A detailed description of dosage schedules employed in the treatment of these patients has been presented elsewhere.[12] Duration of therapy ranged from 22 to 106 days (mean, 47 days) and the maximum doses employed approximated 1 I.U. per pound per day of ACTH, 3 mg. per pound per day of cortisone, and 60 mg. per pound per day of salicylate. For reasons previously stated[4] plasma samples from the patients receiving cortisone were obtained five to six hours after administration of one dose and just preceding the next dose; therefore, the plasma concentrations measured do not represent the peak elevations obtained.[13]

From the Lockhart Memorial Laboratory, Department of Pediatrics, University of Utah College of Medicine, and the State Heart Laboratory of the Utah State Department of Health.

This work was supported in part by grants-in-aid from the American Heart Association, the Helen Hay Whitney Foundation, the Institute for the Study of Analgesic and Sedative Drugs and the A. H. Robins Company.

*Part of this work was done during the tenure of an American Heart Association Research Fellowship.

**Helen Hay Whitney Foundation Fellow.

*Cortone was supplied through the courtesy of Merck & Co., Inc., Rahway.

†ACTHAR GEL was supplied through the courtesy of the Armour Laboratories, Chicago.

OBSERVATIONS

Analysis of the values for the 17-OHCS plasma concentrations and twenty-four-hour urinary excretions demonstrated a characteristic relationship to exist between them in each of the therapy groups, with certain differences in this relationship being apparent among the groups. Fig. 1 compares graphically the effects of various doses of cortisone and ACTH gel on the mean plasma concentrations and urinary excretions of 17-OHCS. In the case of either hormonal agent the plasma steroid concentration and the urinary steroid excretion were directly proportional to the size of the daily dose. The slope of the line representing the relationship between cortisone dose and plasma 17-OHCS concentration is nearly identical to that representing the relationship between cortisone dose and the urinary 17-OHCS excretion. A similar interrelationship among plasma 17-OHCS levels, urinary 17-OHCS excretions, and dose of drug was observed in the group treated with ACTH gel. The difference in these relationships between the cortisone and the ACTH gel groups indicates that each unit of ACTH gel is several times more effective than each milligram of cortisone in producing increases in the plasma 17-OHCS concentration and the urinary 17-OHCS excretion. Inasmuch as the plasma 17-OHCS levels during cortisone therapy were obtained at times which did not represent peak elevations, this comparison might seem unjustified. However, this same objection does not apply to the urinary excretion values, as these do not depend upon the time of sampling.

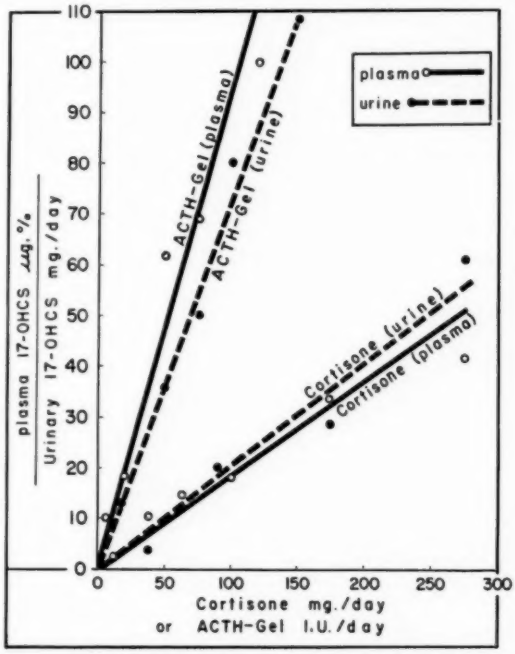

Fig. 1.—Relationship of hormone dose to 17-OHCS value.

In certain individuals the relationship between 17-OHCS levels in plasma and excretions in urine was found to be variable, especially during oral cortisone therapy. This variable relationship is illustrated by the data of four patients presented in Fig. 2 (K. C., Fig. 2, *a*; L. A., 2, *b*; S. B. 2, *c*; V. N., 2, *d*). In two patients (Fig. 2, *a* and *b*) a parallelism exists between the curves for plasma 17-OHCS concentrations and those for urinary 17-OHCS excretions during the period of therapy. This parallelism continues during the immediate post-therapy period, when the elevations of both disappear. On the other hand, in S. B. (Fig. 2, *c*) essentially no plasma 17-OHCS elevations were observed despite a considerable increase in urinary excretion values during the period of therapy. The data of V. N. (Fig. 2, *d*) demonstrate a complete lack of proportionality between plasma levels and urinary excretions of 17-OHCS. These data were obtained during one continuous period when the patient was receiving a daily dose of 200 mg. cortisone orally. Although there were fluctuations of both plasma and urine values during this period, these fluctuations seemed entirely independent of one another. However, for the cortisone-treated group, as a whole, regardless of the relationship which existed between plasma and urinary steroids for individual patients during therapy, the values for both became quite low in the immediate post-treatment period.

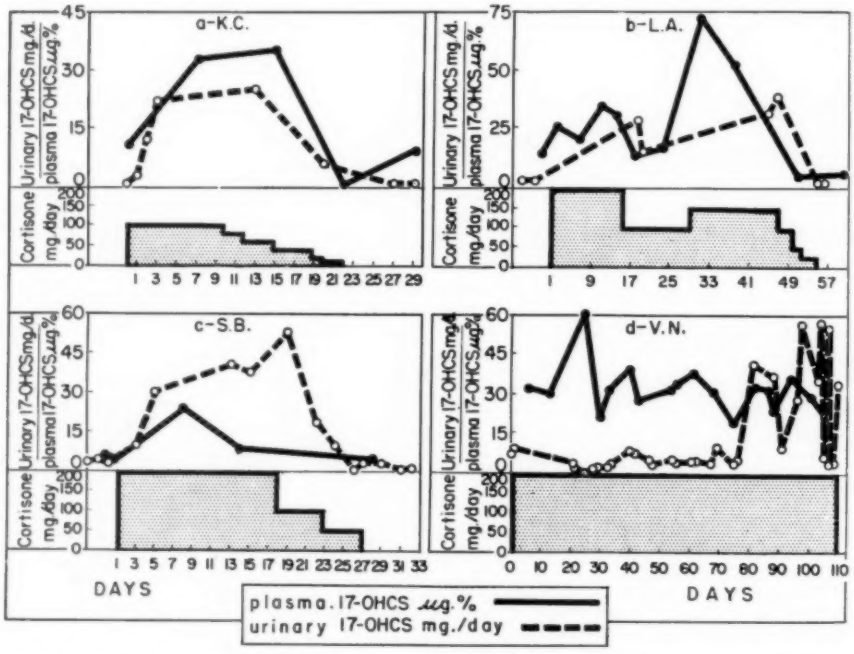

Fig. 2.—Plasma and urinary 17-OHCS values in patients receiving oral cortisone therapy.

During periods of ACTH gel therapy the relationship of plasma and urinary 17-OHCS values in individual patients was found to be more consistent than that found during cortisone therapy. This relationshp is illustrated by the data of two patients presented in Fig. 3, (A. W. Fig. 3, *a*; B. S., Fig. 3, *b*). In patient A. W. (Fig. 3, *a*) large, roughly proportional elevations of plasma 17-OHCS concentrations and urinary excretions occurred during the period of ACTH gel therapy. During the periods of final tapering and discontinuation of ACTH gel dose the plasma and urinary values became very low. The data of patient B. S. (Fig. 3, *b*) illustrate a considerable change in plasma 17-OHCS concentrations and urinary excretions in association with changes in the daily dose of ACTH gel. In this patient, when the daily dose of ACTH gel was reduced on the fortieth day from 90 to 70 mg., a prompt and complete, although temporary, disappearance of both plasma and urinary steroid elevations resulted. In a similar manner these elevations decreased after a small decrement in dose on days 76 and 81,

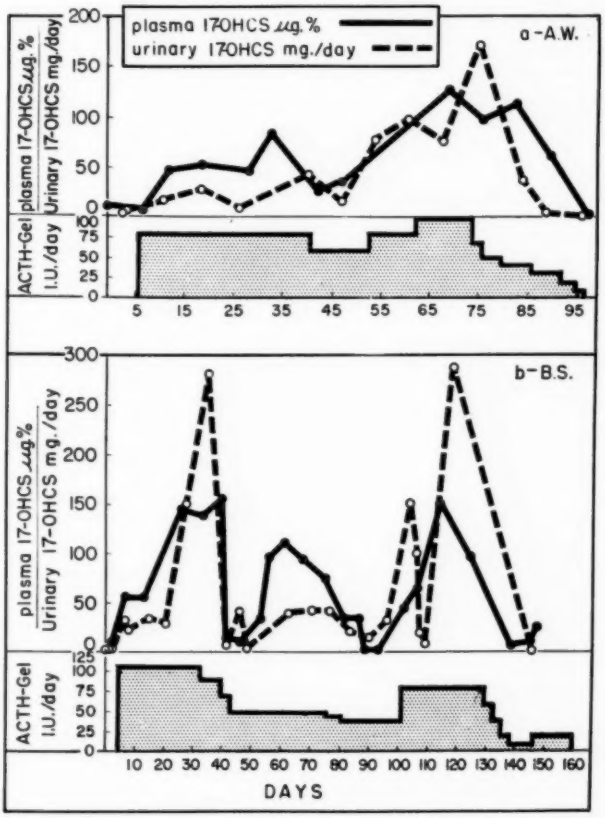

Fig. 3.—Plasma and urinary 17-OHCS values in patients receiving ACTH gel therapy.

and disappeared after a larger decrease in dose on day 130.

In contrast to the observations in patients receiving cortisone or ACTH gel, there were no elevations of plasma or urinary 17-OHCS in patients during periods of salicylate administration. therapy was an elevation noted in either plasma or urinary 17-OHCS, compared with the pretherapy values or with the normal values of 12.0 ± 1.29 μg per cent for plasma,[1] and of 2.2 ± 0.27 mg. per twenty-four hours for urine.[6]

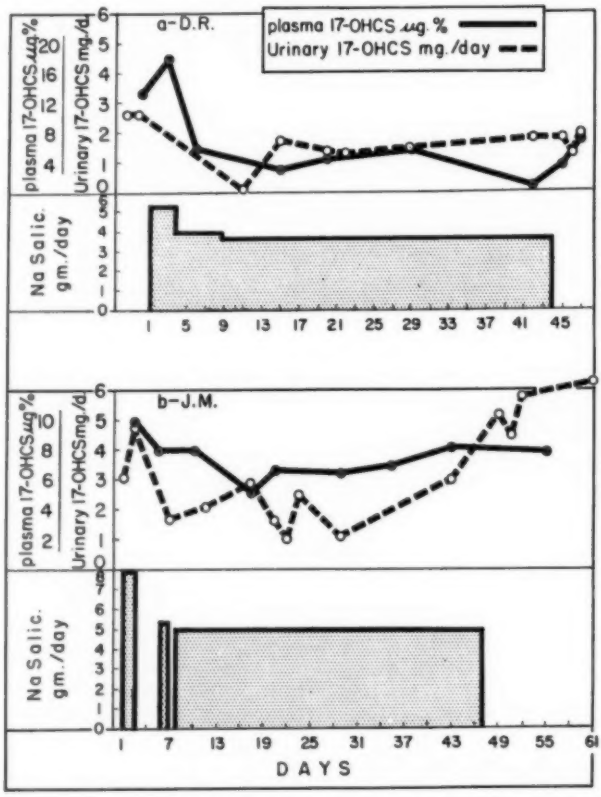

Fig. 4.—Plasma and urinary 17-OHCS values in patients receiving salicylate therapy.

Fig. 4 presents the data of two representative patients (D. R., Fig. 4, *a*, and J. M., Fig. 4, *b*). Serial determinations of 17-OHCS in plasma and in urine were performed during the period of salicylate therapy as well as during the pre- and post-therapy periods. At no time during salicylate

DISCUSSION

The observations reported demonstrate the relationship between plasma 17-OHCS levels and urinary 17-OHCS excretions in patients with rheumatic fever, and the effects of various types of therapy on this relationship. A close correlation was observed between

mean plasma or urinary steroid values and the dose of either ACTH gel or cortisone, although the former was more potent in producing steroid elevations. In patients receiving salicylate therapy the relationship between plasma concentrations and urinary excretions of 17-OHCS did not vary appreciably, since no elevations in either resulted from the therapy. In individual patients receiving cortisone therapy the relationship between plasma 17-OHCS concentrations and urinary 17-OHCS excretions varied more widely than did this relation for patients treated with ACTH gel. Inasmuch as the plasma samples were obtained usually four to six hours after administering a dose of cortisone, the variation in the plasma 17-OHCS levels observed is not surprising, as the expected peak elevation would be at about two hours.[13] Actually, in spite of this individual variation, the overall plasma-urine correlation for cortisone was as good as that for ACTH gel, where sustained plasma 17-OHCS elevations are found following a single injection.[14]

The finding of marked decreases in the steroid plasma concentrations and urinary excretions following small decreases in the daily ACTH gel dose in patient B. S. (Fig. 3, *b*) suggests that adrenal cortical responsiveness is influenced by conditioning factors. In this patient, decreases in the dose of ACTH gel were followed promptly by a temporary disappearance of both plasma and urinary steroid elevations. It seems probable that this lack of adrenal cortical secretory activity following the decrease in ACTH gel dose was occasioned by a temporary and relative adrenal refractoriness ensuing after prolonged stimulation with the previous larger dose. The temporary nature of this refractoriness is indicated by the reappearance of elevations after several days at the same reduced dosage. Its relative nature is indicated by the elevations observed following the subsequent administration of larger daily doses of ACTH gel. This concept of temporary relative adrenal cortical refractoriness occurring with decrease in the dose of administered ACTH provides a physiological rationale for the use of a cautious program of tapering of dose in ACTH therapy. In patient A. W. (Fig. 3, *a*), despite a gradual tapering schedule, there occurred a decrease in plasma and urine 17-OHCS levels to low values during the period of tapering of dose.

As reported previously,[4, 5] following cortisone therapy a similar, but more profound, temporary and relative adrenal cortical refractoriness occurs. This suggests that in tapering cortisone therapy also, the dose should be decreased cautiously.

The relationship of plasma 17-OHCS concentration to urinary 17-OHCS excretion was not altered significantly during periods of salicylate administration. Actually, slight reductions in both occurred during the period of therapy. Inasmuch as previous studies[15-17] have produced evidence suggesting a dual effect of salicylates on adrenal cotrical steroids, causing both increased rate of their production and increased rate of their disappearance from circulation, it seems possible that these decreases in urinary and plasma 17-OHCS during salicylate therapy reflect an increase in utilization. Further investigation is necessary to establish the validity of this concept.

SUMMARY

1. The relationships of plasma 17-OHCS concentrations to urinary 17-OHCS excretions were observed in children with active rheumatic fever treated with oral cortisone, ACTH gel, or salicylates.

2. Elevations of plasma 17-OHCS concentrations and urinary 17-OHCS excretions, proportional to the dose of hormone, were observed during cortisone and ACTH gel therapy; no such elevations occurred during salicylate therapy. ACTH gel was more potent than cortisone, in terms of I.U. ACTH vs. mg. cortisone, in producing the increases in plasma and urinary 17-OHCS values.

3. A temporary relative adrenal cortical refractoriness was observed in patients treated for considerable periods of time with hormones. Because of this it is suggested that a cautious program of tapering the dose be employed.

We are indebted for technical assistance to Doris F. Tippit, H. Beth Dowding, Mary C. O'Brien, Tiona L. Hughes, Helen C. Birch, and Clayton H. DeBruin.

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NEWBORN TEMPERATURE

I. Temperatures of Term Normal Infants

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THE purpose of this investigation was to determine the rectal temperatures of normal term infants during the immediate neonatal period under conditions encountered routinely in a single delivery suite. Although there is general agreement that some infants have a "subnormal" temperature on admittance to the nursery,[1, 2] a review of the literature failed to reveal any continuous temperature records obtained during the first hour of extrauterine life.

PROCEDURE

Immediately following delivery the thermistor element of a "Tele-thermometer"[3] was inserted beyond the rectal sphincter of the newborn infant and temperatures were recorded continuously while the baby was in the delivery room.

PATIENTS AND CONDITIONS

The infants in this series were a select group, in that all of them weighed 2,500 grams or more, had normal, spontaneous, and continuous respirations, and were studied on the Negro obstetrical service of Emory University at Grady Memorial Hospital. The management of labor and/or delivery was not altered in any way because of this study.

Description of Delivery Suite.—The delivery suite is continuously air conditioned by an air-conditioning unit equipped with Johnson controls and has a constant relative humidity of 52 per cent (±2) at 74° F. During the period of this investigation delivery room temperatures ranged from 70° to 80.1° F., but eighteen of the twenty-three infants were delivered at room temperatures between 73° and 77° F. The average room temperature was 75.6° F.

Delivery Room Procedure.—Deliveries were performed by obstetrical resident physicians, interns, and medical students. Immediately following delivery the infant's upper respiratory tract was cleared, the umbilical cord was divided between clamps, and the baby was placed uncovered on the instrument table behind the physician. Silver nitrate was then instilled into the eyes, a cord clamp applied, and the infant handed to a nurse who wrapped him in a nonfleecie cotton wrapper, weighed him, and placed him in a bassinet heated by electric light bulbs. The majority of the babies had dry skin by the time they were passed to the nurse. Bassinet temperatures were usually the same as, but occasionally were slightly higher than, room temperatures.

From the Department of Obstetrics and Gynecology, Emory University School of Medicine, and Grady Memorial Hospital.

RESULTS

Continuous temperature records were obtained from twenty-two normal term infants delivered vaginally and one term infant delivered by elective cesarean section. For purposes of this paper, the babies are divided into groups according to the two greatest variants of labor and delivery. These variants are analgesia and/or anesthesia versus nonmedicated labors and/or deliveries (Table I). The temperatures of these infants are shown in Figs. 1, 2, 3, and 4.

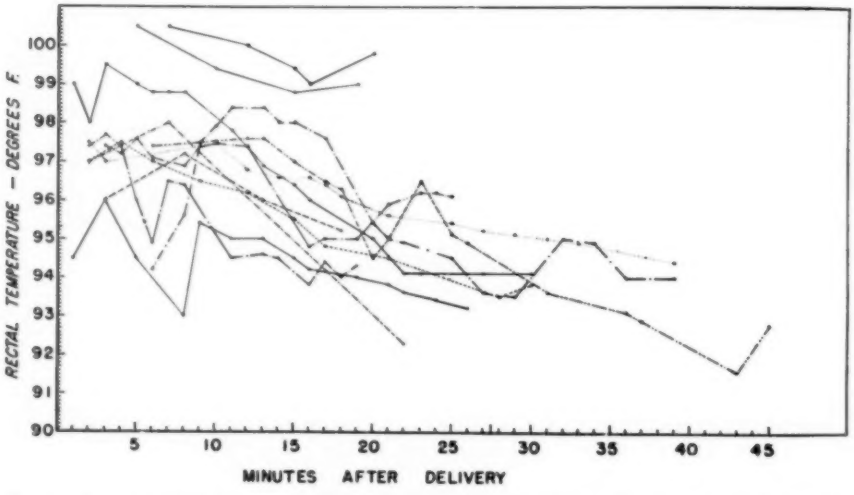

Fig. 1.—Rectal temperatures of infants delivered from mothers who had no analgesia or anesthesia.

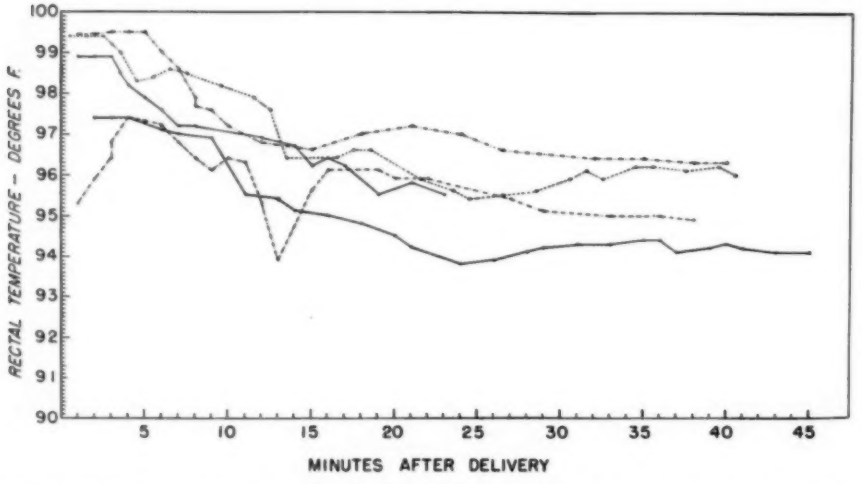

Fig. 2.—Rectal temperatures of infants delivered from mothers who had clinically inadequate analgesia and no anesthesia.

TABLE I. MANAGEMENT OF LABOR AND DELIVERY

MANAGEMENT	NO. OF PATIENTS
Without analgesia or anesthesia	12
With clinically inadequate analgesia and without anesthesia	5
With clinically adequate analgesia and without anesthesia	4
Without analgesia and with general anesthesia	2
Total	23

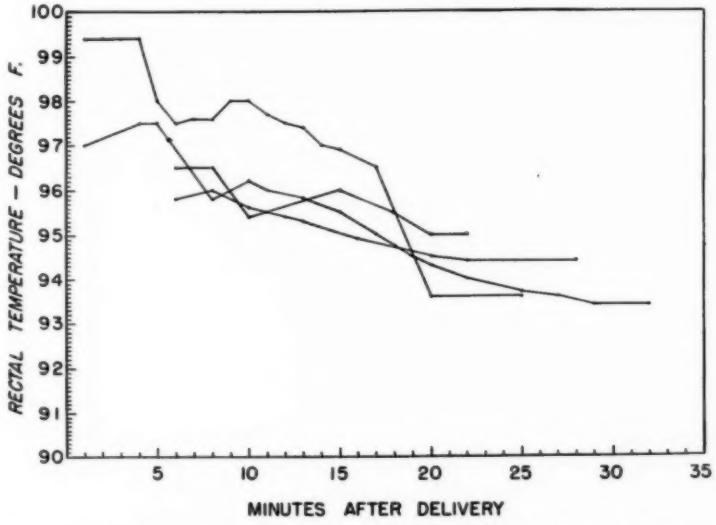

Fig. 3.—Rectal temperatures of infants delivered from anesthetized mothers.

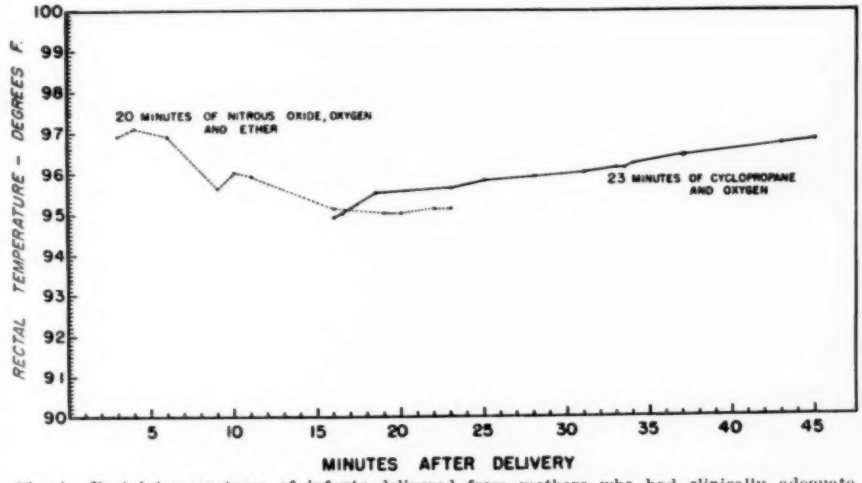

Fig. 4.—Rectal temperatures of infants delivered from mothers who had clinically adequate analgesia and no anesthesia.

DISCUSSION

The figures graphically illustrate that: (1) the temperature of term, normal, newborn infants is lower than is generally appreciated and may fall suddenly and precipitously to these levels; (2) temperatures vary widely from infant to infant, and a single temperature recording during the immediate neonatal period is indicative of the infant's temperature status for only a fleeting moment; (3) although almost all of the infants in this series had a decrease in temperature, the internal environment can be defended momentarily as illustrated by a rise in temperature; (4) there is no marked difference in the temperature trend of the various groups (Table I).

Some of the temperatures found in this group of normal infants were so low that were the infants in a nursery, they might very well have been placed immediately in a heated incubator. Critical observation failed to reveal any apparent cause for the rapid (as great as 1.4° F. per minute) decreases in temperature. The decreased breath frequencies observed concomitantly with decreased temperatures in newborn animals,[4] could not be confirmed visually in this group of human newborn infants. Neither cyanosis nor shivering occurred in any of the infants studied.

The maintenance of a constant temperature at a "normal" level is necessary for the well-being of the human adult, but the belief that the newborn infant must be placed in a warmed environment and the necessity of maintaining newborn temperatures at a high level is based primarily on teleological thought. Decreased temperatures and temperature fluctuations may be desirable or even essential for a rapid and satisfactory adjustment to extrauterine life. Since mature babies exhibit such variable temperatures, it might be predicted that the premature infant would exhibit the same or even greater changes. This problem is currently under investigation.

An occasional and inconstant temperature rise was noted at the time when the cord clamp was applied and silver nitrate solution instilled into the eyes and during periods of crying and somatic activity. Some of the most precipitous falls in temperature occurred during periods of activity, and significant temperature rises were observed at times when the babies were perfectly quiet. Failure of a marked temperature rise as the babies changed from a period of quiet inactivity to a period of marked activity, during crying, lacks an adequate explanation especially since other investigators have stated that periods of intense muscular activity may increase heat production by as much as 100 per cent above that at rest.[5] The rapid temperature fluctuations make it difficult to accept any concept of basal metabolism per se during the first hour of life.

Comparison of the temperature curves shown in Fig. 1 finds no significant variation in the type of temperature curve. Nor can actual gestational age, sex, quantity of sedation, actual room temperature at the time of delivery, or the infant's over-all activity be used as a common divisor.

SUMMARY

Continuous rectal temperature records of twenty-three normal term infants were obtained during the immediate post-delivery period. The tem-

perature curves of individual infants showed marked fluctuations which could not be correlated with crying and/or other physical activity.

Although all infants exhibited poikilothermia to some degree, they nevertheless had the ability to increase their rectal temperatures momentarily.

No marked difference was noted in the temperature curves of babies born of unsedated, sedated, and anesthetized mothers.

Examination of the data suggests that decreased temperatures and temperature fluctuations may be desirable or even essential for a rapid, satisfactory adjustment to extrauterine life.

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Multiple Births

We hear from Danbury, that last week the wife of Benjamin Starr, of that place, was safely delivered of three male children, one on Thursday, and two on the Saturday following. The first died a few hours after its birth, the other two appear likely to live. She has had two children at a birth once before: is now in the 29th year of her age, the mother of nine living children, the eldest little more than 10 years of age; is herself a twin, one of 15 children born of the same mother, who died before she was forty years of age.

NEW LONDON GAZETTE, SEPT. 23, 1774.

January 30, 1789. This day a woman by the name Welch was delivered of Twins in the South fields & died after delivery. One child has survived her. This is the fourth time of bearing twins & the woman is now possessed of no lawful husband & 46 years of age. Weight 300 lbs.

DIARY OF REV. WILLIAM BENTLY OF SALEM. SALEM, 1905.

COARCTATION OF THE AORTA WITH PATENT DUCTUS ARTERIOSUS

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ST. LOUIS, MO.

COARCTATION of the aorta in infants may be the cause of cardiac failure and death. According to Calodney and Carson[6] it is the most common cause of cardiac failure in infants under 2 months of age. Although the classical "adult" type is usually easily recognized, the diagnosis is infrequently made in infants. Since little has been written about the radiologic features of coarctation of the aorta associated with patent ductus arteriosus, we would like to present our experience with this entity and discuss the problems of clinical and radiographic diagnoses.

The classification of coarctation of the aorta into adult and infantile types as suggested by Bonnet[4] has led to considerable confusion. Cases in which there is a short segment of constricted aorta occurring at or just distal to the insertion of the ligamentum arteriosum are considered to be adult in type, while those in which the constricted segment is long and involves the region of the fetal isthmus (the segment from the origin of the left subclavian artery to the insertion of the ductus arteriosus) are included in the infantile group. However, the adult type can occur in infants and the infantile type occurs in adults, and neither term suggests the type of abnormal circulation or the prognosis.

From the Edward Mallinckrodt Institute of Radiology and the Department of Pediatrics, Washington University School of Medicine.

In 1933, Evans[8] proposed a new classification based upon patency of the ductus arteriosus as well as the site and extent of the coarctation. Calodney and Carson defined the infantile type as that in which the coarcted segment was diffuse and proximal to a patent ductus arteriosus, while in the adult type there was a shorter constricted segment occurring just at or distal to a closed ductus arteriosus. More recently Johnson and associates[13] have suggested the following classification based on anatomic and hemodynamic considerations arising from the status and site of the ductus and the adequacy of the collateral circulation. Edwards[7] has also suggested a similar classification:

I. Coarctation of the aorta with a closed ductus arteriosus
   1. With collateral circulation
   2. Without (or with inadequate) collateral circulation (incompatible with life)

II. Coarctation of the aorta with a patent ductus arteriosus
   1. Proximal to coarctation
      a. With collateral circulation
      b. Without (or with inadequate) collateral circulation (incompatible with life)
   2. Distal to coarctation
      a. With collateral circulation
         (1) Pressure maintained by collateral circulation adequate to prevent flow from pulmonary artery into aorta

(2) Pressure maintained by collateral circulation inadequate to prevent flow from pulmonary artery to aorta

b. Without collateral circulation

We have reviewed our files and have collected twelve examples (including three cases previously reported by Calodney and Carson) of coarctation of the aorta associated with a patent ductus arteriosus that have had roentgenographic examinations and were proved by either surgical exploration or post-mortem examinations. In five patients an angiocardiogram was done. Two additional cases had angiocardiographic confirmation only.

COARCTATION OF THE AORTA DISTAL TO THE AORTIC MOUTH OF A PATENT DUCTUS ARTERIOSUS

When the coarcted aortic segment is distal to the aortic opening of a patent ductus arteriosus, there is no communication with the descending aorta except by way of collateral circulation which is usually well developed. Because of the higher pressure in the proximal aortic segment, the flow of blood through the ductus is from the systemic into the pulmonary circulation. Clinically the presence of a diastolic murmur should suggest this possibility in adults but this murmur is rare in infants. Differentiation of a bicuspid aortic valve with insufficiency may be difficult.[5] Taylor and coworkers,[19] describing their results of cardiac catheterization in this condition, stated that although pulmonary hypertension was present, it was considerably lower than the systemic arterial pressure in the lower extremities. Bahn and associates[2] described two cases studied pathologically in which the pulmonary arteries showed medial hypertrophy, and adventitial fibrosis associated with luminal narrowing. Since a normal oxygen saturation in the femoral artery was found, this supported the view that no right-to-left shunt existed. The chest film usually shows moderate cardiac enlargement with varying degrees of pulmonary vascular engorgement. The following case is representative of this type of anomaly.

CASE 1.—N. E. K. was a 7-month-old white female infant who entered the hospital because of a twenty-four-hour history of difficult breathing. Examination revealed a pale, acutely ill infant with rapid grunting respirations and fever. Tachycardia was present, but no cardiac murmurs were heard. Twenty-four hours following hospital entry, the infant was found to be apneic, cyanotic, flaccid, and vomiting bright red blood. The femoral pulsations were markedly diminished. The systolic blood pressure in the right and left arms ranged from 140 to 160, while in the leg it was 55 to 70. Digitalization and oxygen therapy resulted in gradual improvement.

Chest roentgenograms (Fig. 1) revealed moderate cardiac enlargement with elevation and rounding of the apex suggesting right ventricular enlargement. Pulmonary vascular engorgement was present, suggesting hypertension in the lesser circulation.

Retrograde angiocardiography was performed by injecting 6 c.c. of 70 per cent Urokon into the left subclavian artery. A well-defined, short, constricted aortic segment was visualized. Contrast material was also observed in the pulmonary arterial system, denoting patency of the ductus arteriosus. A well-developed collateral circulation involving the internal mammary and intercostal arteries was also demonstrated.

Comment.—In the absence of surgical or autopsy verification, it is impossible to accurately classify this pa-

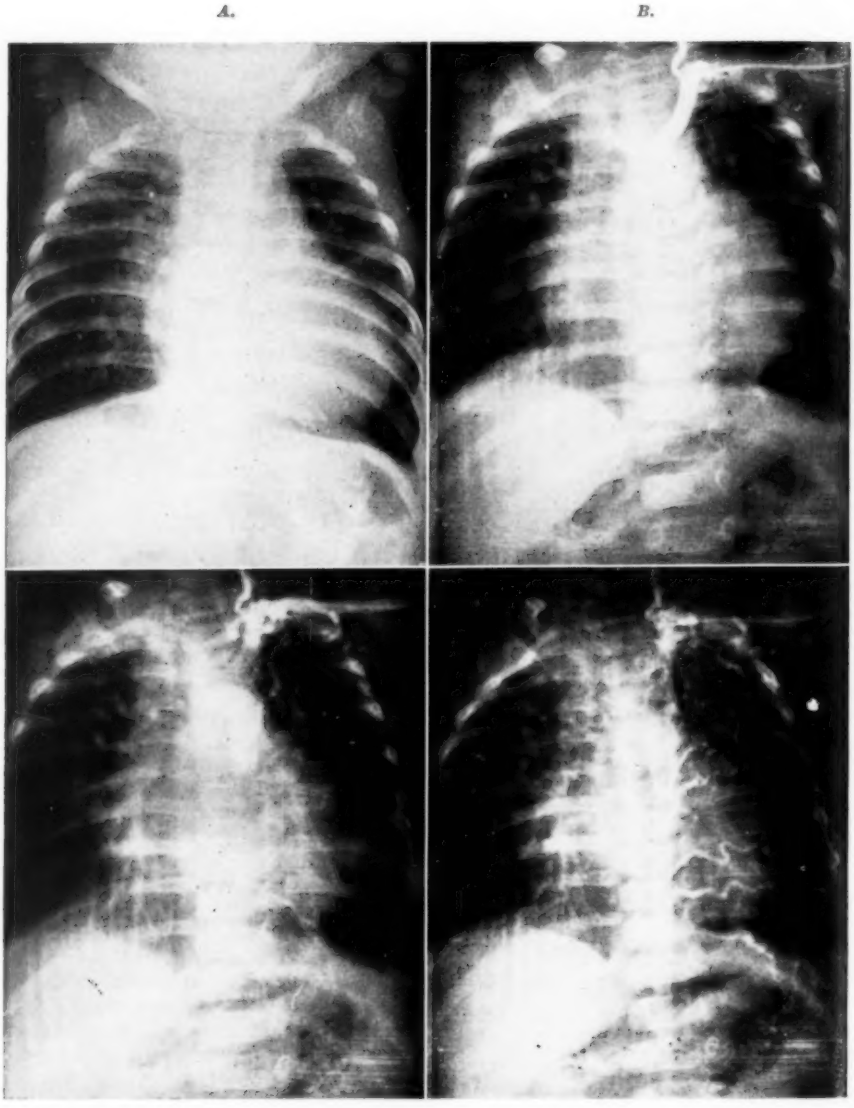


Fig. 1.—*A*, Conventional roentgenogram of Case 1 showing right ventricular cardiac enlargement and pulmonary vascular engorgement. *B*, Beginning of retrograde aortogram demonstrating a dilated L subclavian artery. *C*, Film exposed one second later demonstrating the site of aortic narrowing and opacification of pulmonary arteries denoting patency of the ductus arteriosus. *D*, Opacification of coarctation, descending aorta, and collateral circulation.

tient. The angiocardiographic evidence of coaretation and patency of the ductus arteriosus seems quite definite, but the localization of the ductus with relation to the coarcted segment is not clear. The presence of a left-to-right shunt and a well-developed collateral circulation favors a postductal coaretation. Several instances of coaretation of the aorta distal to a patent ductus arteriosus with collateral circulation have been reported.[7, 9, 12, 18, 19] This combination of a patent ductus arteriosus located proximal to aortic coaretation is compatible with a fairly long survival and is amenable to surgical correction. Fawcett's[9] patient lived forty-five years. Taylor and associates[19] described a 27-year-old male with this condition in whom the ductus was divided and the coaretation successfully excised. These authors also reported improvement of blood flow to the descending aorta in a 16-year-old male following closure of the ductus without excision of the coaretation. Jonsson and co-workers,[14] in their monograph on thoracic aortography, included two patients, aged 13 and 14, in whom retrograde aortography demonstrated a patent ductus proximal to an aortic coaretation. They mentioned nine other patients with a patent ductus that were not diagnosed by aortography, but the lumen of the ductus was very small and probably not of clinical significance.

COARCTATION OF THE AORTA PROXIMAL TO THE AORTIC MOUTH OF A PATENT DUCTUS ARTERIOSUS

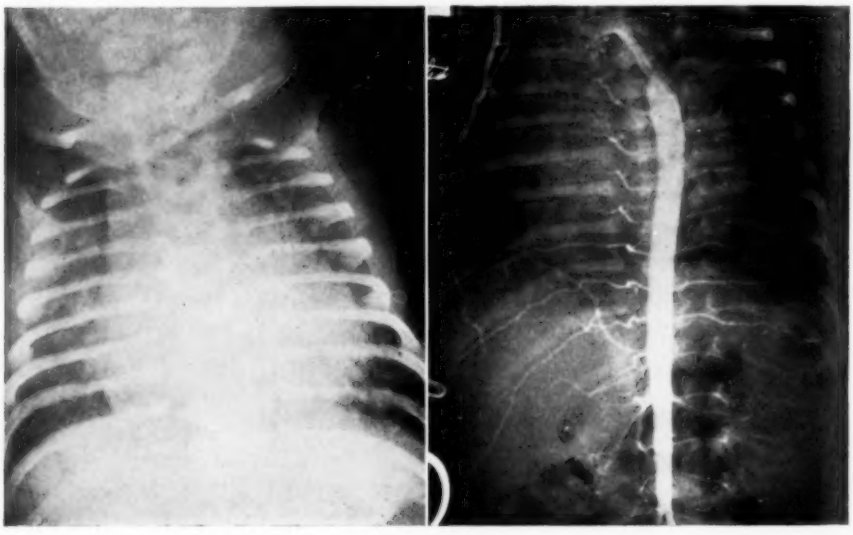
In this situation there is free communication via the patent ductus between the pulmonary artery and the descending aorta. It has been hypothecated[2, 6] that since this is the normal pathway during fetal life there is no stimulus for the development of a collateral circulation before birth. Because of the pressure gradient the right ventricle pumps blood into the descending aorta with resultant hypertrophy and dilatation as found in many of the patients reported by Calodney and Carson. This right-to-left shunt is the cause of the cyanosis observed clinically, which occasionally may be more marked in the lower extremities.

Review of the conventional roentgenograms of the chest of this group reveals two significant abnormalities; moderate to marked right ventricular cardiac enlargement and dilatation and engorgement of the pulmonary vessels. Even in the absence of congestive failure the large pulmonary vessels reflect the pulmonary hypertension and increased pulmonary blood flow that must exist with this anomaly. The following three cases illustrate some of the major clinical and radiologic features of this type of coaretation.

Case 2 (Reported by Calodney and Carson).—H. W., a male infant, appeared perfectly normal until the eighth day of life, when cyanosis of the extremities was noted. Examination revealed cyanosis, rapid respirations, and a few fine basilar râles in both lungs. A harsh systolic and a low-pitched diastolic murmur were heard in the third left interspace. There was moderate hepatomegaly and splenomegaly. Faint femoral pulsations were palpable. The blood pressure was 100/80 in both arms and was not obtainable in the legs.

Conventional roentgenograms of the chest (Fig. 2, *A*) showed moderate enlargement of the cardiac silhouette that suggested right ventricular predominance. There was moderate pul-

monary vascular engorgement compatible with pulmonary hypertension. Retrograde aortography via the left common carotid artery revealed a diffuse type of coaretation beginning just distal to the left subclavian artery (Fig. 2, *B*). There was no flow of contrast material into the pulmonary circulation and there was no angiographic evidence of a well-developed collateral circulation. A few minutes after the angiogram, respirations ceased.



A. *B.*

Fig. 2.—*A*, Chest roentgenogram of Case 2 demonstrating right ventricular cardiac enlargement and pulmonary vascular engorgement. *B*, Retrograde aortogram via the L common carotid artery revealing a diffuse coarctation. The angiogram failed to demonstrate the patent ductus probably indicating that the shunt was from right to left.

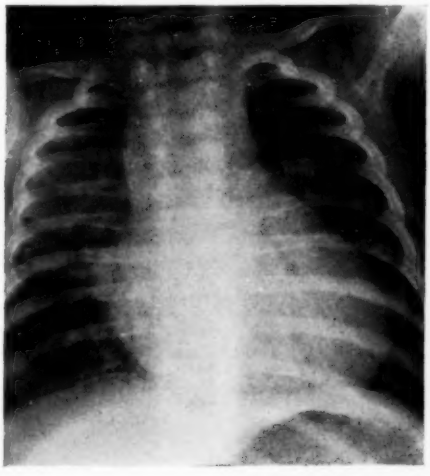
At autopsy there was evidence of right ventricular hypertrophy. The aortic ring measured 19 mm. in circumference. Just distal to the left subclavian artery the aorta narrowed to 3 mm. in diameter as compared with a diameter of 11 mm. in the ascending aorta. The coareted segment ended at the orifice of a patent ductus arteriosus measuring 12 mm. in circumference.

Comment.—The fact that the opaque contrast material injected into the aorta did not flow into the pulmonary circulation suggests that the pressure gradient was directed in the opposite direction. This supports the view that the right ventricle acts as a systemic ventricle in this condition and pumps blood into the systemic circulation via the pulmonary artery, a patent ductus arteriosus, and descending aorta. The failure to demonstrate the patent ductus arteriosus illustrates the limitations of retrograde aortography in this type of malformation.

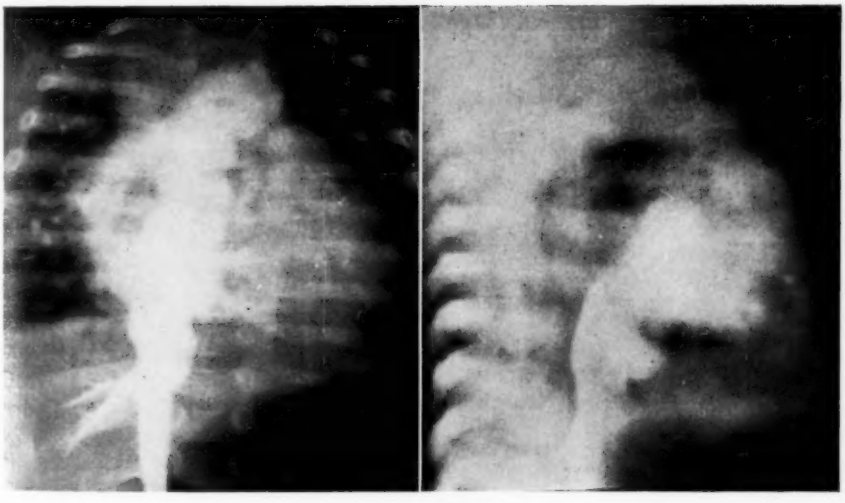
CASE 3.—M. S., a 3-month-old white male infant, was admitted to the hospital with a history of difficult swallowing since the tenth day of life. At that time it was also noted that the infant became cyanotic with crying and the cyanosis involved the face and sometimes the arms. When the infant was seen in the clinic the systolic blood pressure by the flush technique was

found to be 121 in the arms and 62 in the legs. While manipulating the infant for fluoroscopy and roentgenograms, the entire body became cyanotic.

Examination at the time of hospital entry disclosed a well-developed, well-nourished, ashen-colored male infant with a weak cry. The following systolic blood pressures were obtained: right



A.



B. *C.*

Fig. 3.—*A*, Chest roentgenogram of Case 3. Cardiac enlargement and minimal pulmonary vascular engorgement. *B*, Anteroposterior view of intravenous angiocardiogram revealing opacification of right heart, pulmonary artery, and descending aorta. Note absence of filling of ascending aorta and brachiocephalic arteries. *C*, Lateral view of intravenous angiocardiogram exposed simultaneously with *B*.

arm, 62; left arm, 64; right leg, 60; left leg, 56. Subsequent determinations varied between 76 and 88 in all four extremities. The lungs were clear. The heart was enlarged by percussion and the heart sounds were of poor quality. A grade 2 precordial systolic murmur transmitted to the neck and axilla was heard. It was noted that, on crying, the arms first became cyanotic and later the lower extremities. An electrocardiogram was interpreted as sinus tachycardia, hypertrophy and/or dilatation of the left ventricle. Roentgenograms of the chest showed moderate cardiac enlargement involving right and left ventricles with minimal pulmonary vascular engorgement (Fig. 3, *A*).

Intravenous angiocardiography was carried out without incident. The contrast material filled the right heart with almost simultaneous opacification of a dilated pulmonary artery and the descending aorta (Fig. 3, *B* and *C*). The appearance in the lateral view simulated opacification of the ascending and transverse aortic arch and suggested the diagnosis of transposition of the great vessels. In retrospect this opinion was not valid because of the absence of filling of the large brachiocephalic arteries which arise from the aortic arch. Several days later the infant developed a respiratory infection and died.

At autopsy the heart weighed 55 grams and showed hypertrophy and dilatation of both chambers. A 6 by 12 mm. defect of the membranous portion of the interventricular septum was present. The aortic ring was small (18 mm. circumference) and the valve was bicuspid. The circumference of the ascending aorta was 24 mm., but narrowed to 10 mm. just distal to the right carotid artery. This narrowed segment ended just distal to the left subclavian artery. The ductus arteriosus was patent (7 mm. diameter) and inserted just distal to the coaretation. The only other anomalies were a 3 mm. diameter patent foramen ovale of the guarded type and a dilated pulmonary artery measuring 40 mm. in circumference.

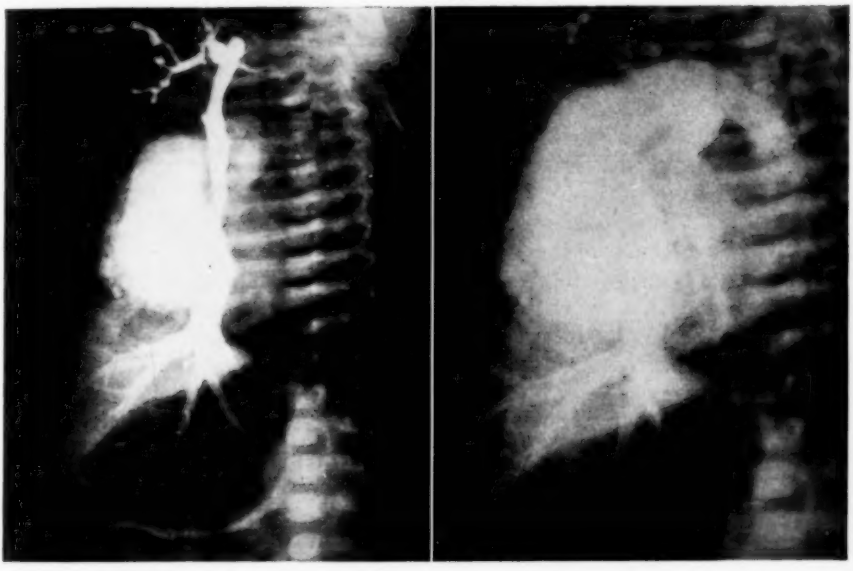
CASE 4.—C. A. D., a 6-week-old white male infant, entered the hospital because of paroxysmal cough since birth. Examination revealed a well-developed and well-nourished infant with no evidence of cyanosis or clubbing. A systolic murmur was heard in the region of the left second and third interspaces. The blood pressure by the flush technique was found to be 110 to 125 in the arms, and 75 to 80 in the legs. There was no palpable femoral pulses. Laboratory data revealed a 4.4 million red cell count with 14 grams of hemoglobin.

Roentgen examination of the chest revealed moderate cardiac enlargement with right ventricular preponderance and evidence of pulmonary vascular engorgement. In order to confirm the clinical impression of coaretation of the aorta, intravenous angiocardiography was performed under ether anesthesia. A test dose of 50 per cent Diodrast was injected intravenously with no immediate reaction. Ten cubic centimeters of 50 per cent Diodrast was then injected and serial films exposed. The angiocardiogram showed sequential opacification of the right auricle, right ventricle, pulmonary artery, and descending aorta (Fig. 4, *A* and *B*). It was not until 4 to 5 seconds later in the cycle that the left heart was visualized. There was no immediate reaction to the injection of the contrast material. Ten minutes following the injection, the child became pale, pulseless, and respiration ceased.

Comment.—Although no post-mortem examination was done, the blood pressure differential between the upper and lower extremities strongly supported the diagnosis of coaretation of the aorta. The presence of a patent ductus distal to the coaretation was strongly supported by the roentgenographic evidence of right ventricular cardiac enlargement associated with

pulmonary vascular engorgement and the angiocardiographic evidence of sequential opacification of right ventricle, pulmonary artery, and descending aorta. The angiocardiographic findings in this case were identical with those of Case 3.

pressure in the pulmonary circulation. These findings contrast sharply with the clear lungs and left ventricular hypertrophy seen in uncomplicated cases of coarctation of the aorta. Marks and associates[16] described the findings in a 2-day-old infant with coarctation



A. *B.*

Fig. 4.—*A*, Lateral view of angiocardiogram of Case 4 showing visualization of the right heart and main pulmonary artery. *B*, Angiocardiogram one-half second following *A* showing opacification of pulmonary artery and descending aorta via a patent ductus arteriosus.

ROENTGENOGRAPHIC FEATURES

Review of the conventional roentgenograms of the twelve autopsied cases revealed moderate to marked cardiac enlargement in all. In most instances, the elevated rounded apex of the cardiac silhouette in the frontal projection and the anterior prominence of the heart in the oblique and lateral views strongly suggested right ventricular enlargement. All of the cases showed definite enlargement of the pulmonary vascular shadows indicative of increased blood flow and/or

and a patent ductus correctly diagnosed during life by roentgenographic evidence of pulmonary vascular congestion and an indentation in the lateral margin of the descending aorta. In most of our cases the shadow of the aortic arch could not be identified on the conventional films. The presence of pulmonary vascular engorgement does not necessarily indicate a right-to-left shunt since it also occurs when the patent ductus is proximal to the coarctation and the shunt is from left to right (Case 1).

Angiocardiography is the most accurate method of differential diagnosis, but is not without hazard in infants who are in critical condition. Two immediate deaths occurred in the four cases subjected to this procedure, both in cyanotic infants with a coaretation proximal to a patent ductus allowing a right-to-left shunt. If the coaretation is distal to a patent ductus, the hazard of angiocardiography may be less. Jonsson and associates[14] reported on the use of thoracic aortography in forty-one patients with coaretation of the aorta, including three cases associated with a patent ductus without a fatality. We do not recommend the routine use of angiocardiography in coaretation of the aorta, but it may yield valuable confirmatory evidence when the clinical diagnosis is not firmly established. The pathologic anatomy and physiology must be kept in mind in selecting the route of injection of the contrast material. When the coareted segment lies distal to the patent ductus, a retrograde injection will demonstrate the narrowed aortic segment and the opacification of the pulmonary arterial system will indicate the presence of a patent ductus (Case 1). However, when the coaretation lies proximal to the patent ductus, the pressure gradient may not permit flow from the aorta into the pulmonary artery and thus no evidence of the patent ductus will be obtained (Case 2). In this instance, the intravenous route is the method of choice, and the flow of contrast material from the pulmonary artery to the descending aorta may be observed (Cases 3 and 4).

CLINICAL ASPECTS

Coaretation of the aorta in infancy is not rare. Carson and Calodney reported twenty-one cases seen at the St. Louis Children's Hospital from 1938 to 1949 and since then twenty-one additional cases have been seen.[11] It is of interest to point out that in infants the association of a patent ductus with coaretation is a common one, occurring in Carson and Calodney's series in nineteen of twenty-one patients and in eleven of twenty-one patients in this series.[11]

The clinical diagnosis of coaretation of the aorta in infancy may be quite difficult and the critical status of the patient does not facilitate the complete examination necessary for diagnosis. The flush technique of blood pressure determination has been very helpful.[10] We have found that the presence of a gradient of 20 mm. Hg or more between the upper and lower extremities is usually indicative of a coaretation. We have, however, seen exceptions. M. S. (Case 3) demonstrated the gradient initially, but this subsequently disappeared. This may be explained on the basis of probable left ventricular failure and the inability of a failing left ventricle to keep up the hypertension seen initially. The presence of femoral pulsations does not rule out coaretation of the aorta. We have seen a number of cases of preductile coaretation with patent ductus arteriosus where the pressures in the lower extremities were 80 mm. Hg or greater. This certainly is in the range of usually encountered systemic pressures in the lower extremities so that femoral pulsations may be present. It is in this type of coaretation that the right ventricle acts as a systemic ventricle and shunts blood from right to left through a patent ductus arteriosus. On several occasions we have observed differential cyanosis between

the upper and lower extremities and in one case we demonstrated lowered blood oxygen saturation in the lower extremities. Thus, this laboratory procedure may be used in conjunction with the "flush" blood pressure technique to help establish the diagnosis of preductile coarctation of the aorta with a patent ductus arteriosus.

The difficulties encountered in diagnosis are minor compared to the difficulties encountered in the therapeutic approach. The prognosis for most infants with coarctation of the aorta with patent ductus arteriosus is very poor. Medical management in our hands has been ineffective. The opinion of some authorities that most infants with coarctation of the aorta can be managed medically and operated upon at a later age has not been true in our experience. All of the patients reported by Carson and Calodney died despite medical therapy.

In our more recent series the results are equally disappointing. Sixteen were treated medically and died, five died during an attempt at surgical correction. Nouaille and co-workers[17] reported that eight out of ten patients not operated upon were dead. We still feel that there is more hope in surgical intervention. There are now several case reports in the literature in which resection of the coarcted segment and division of the patent ductus was successfully performed, followed by marked clinical improvement.[3, 14, 17]

SUMMARY

1. Coarctation of the aorta associated with a patent ductus arteriosus is not a rare congenital anomaly and frequently results in cardiac failure and death.

2. The radiographic appearance of infants with coarctation of the aorta associated with a patent ductus arteriosus has been described.

3. Although the diagnosis may be difficult, a correct clinical diagnosis can be made by the use of flush blood pressure technique, blood oxygen studies, and conventional roentgenograms.

4. Angiocardiography offers confirmatory evidence, but should be used only if the clinical diagnosis is not firmly established.

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PAROXYSMAL TACHYCARDIA DUE TO EPHEDRINE TOXICITY

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THIS is a case history of a 2½-year-old white male treated for paroxysmal tachycardia brought on by the excessive use of ephedrine as part of the treatment of bronchial asthma.

CASE REPORT

J. G., a 2½-year-old white male was admitted to Fordham Hospital on Jan. 24, 1951, because of restlessness and vomiting. In the past, milk and orange juice were known to produce an erythematous rash and stomach cramps. Intermittent attacks of wheezing had recurred for one year. Ephedrine had not been given for its treatment.

Family History.—The father, who has myasthenia gravis, is sensitive to ephedrine and to Prostigmin, and cannot be treated with these drugs. The paternal grandfather had asthma and a maternal aunt has hay fever. The mother has colitis.

Present Illness.—The child had been well until three days prior to admission when he developed rhinorrhea, cough, and wheezing. The following is a record of treatment prior to admission:

January 21: Rhinorrhea, cough, and wheezing.

January 22 and 23: Oral penicillin (amount not known), aminophylline suppositories, gr. 3¾ every six hours. No relief.

January 23: Temperature rose to 101° F. Diffused scattered wheezes and signs of right lower lobe pneumonia appeared. Therapy included: A capsule containing ephedrine sulfate gr. ⅜; theophylline, gr. 1½; phenobarbital gr. 3/16, given orally 1- to 3-hour intervals; and penicillin 300,000 units I.M. After 10 hours of wheezing, a suppository of the same drug was inserted into the rectum. Restlessness increased and intermittent vomiting began. One hour later gr. 1½ sodiumpentobarbital was inserted into the rectum. Three hours later (9 P.M.) 3 gr. sodium pentobarbital was again inserted into the rectum; restlessness and vomiting continued. At 11 P.M. a second suppository of ephedrine, theophylline, and phenobarbital was administered.

January 24 (Date of admission): 1 A.M.—vomiting stopped, restlessness became more marked. 3:40 A.M.—sodium phenobarbital, 2 gr. I.M., no noticeable effect observed. Shortly afterward, vomited coffee-ground material. He was then admitted to Fordham Hospital.

Examination on Admission.—On admission, the child was restless and irritable; the skin was cold, clammy, and pale. Respirations were rapid and shallow. The temperature was 105° F.; the pulse was 200 and the respirations 102 per minute. The pupils were widely dilated and did not react to light. The right eardrum was slightly reddened. The alae nasi were flaring. The pharynx was injected, and the mouth was covered with coffee-ground vomitus. The tonsils were enlarged and injected. The heart rhythm was regular. Scattered wheezes were heard throughout both lungs; dullness, diminished breath sounds and râles were found over the right base anteriorly and posteriorly. The liver and spleen were not palpable.

Course in Hospital.—For the patient's course in hospital and treatment, see Table I.

REVIEW OF LITERATURE

Lapin and Weichsel[1] observed at intervals of about ten minutes tonic contractions of the body musculature,

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restlessness, tachycardia, and dilated pupils due to toxic effects of ephedrine in a 5-month-old child.

In two children, one aged 12 and the other 6, Scott[2] observed tachypnea, tachycardia, and extreme restlessness after moderate amounts of ephedrine had been taken. In one of these death followed the ingestion of approximately three times the amount of ephedrine and theophylline given to the child we observed. The postmortem examination in their case showed many hemorrhages in the brain and in the mucosal membranes. They conclude that the early signs

TABLE I. COURSE IN HOSPITAL

TIME	TEMPERATURE	RESPIRATION PER MINUTE	PULSE	BLOOD PRESSURE	COURSE
On admission	105° F.	102	200		Barbiturates, procaine penicillin, oxygen by tent, 5% glucose in saline, I.V. Regular rhythm
5 hr. later	103.8° F.	70	220		
10 hr. later	100° F.	58	180		
12 hr. later	100.6° F.	60	150		Appeared to be better
17 hr. later		52	160		Child was comfortable
19 hr. later		50	280	68/50	Increasingly apprehensive, liver edge felt 3 to 4 fingerbreadths below costal border. ECG showed regular tachycardia with a rate of 280-300/min., and indicates intraventricular conduction disturbance of the bundle branch block type

TREATMENT	EFFECT ON TACHYCARDIA
Eyeball pressure, carotid sinus pressure	No effect—child comatose
Prostigmin 0.16 mg. I.V.	No effect
Carotid pressure applied	No effect
0.3 mg. lanatoside C I.V. drip	
Eyeball pressure applied	No effect
20 min. later—0.2 mg. lanatoside C I.V.	
After 5 min., eyeball pressure	Marked drop in cardiac rate rhythm essentially regular and interrupted occasionally by irregularly spaced beats. Rate 180/min. Bigeminy and trigeminy appeared. ECG showed ventricular complexes remained wide and P waves could not be identified
5 min. later eyeball pressure ECG taken	Heart rate 150/mm. Definite P waves recognized to precede each ventricular complex. Blood pressure 100/50, skin warmer and more moist
Oxygen for 12 hr. until next morning	Temperature 99.4° F., pulse 124/min. respirations 44/min. Felt well, not restless.
Additional week—signs of pneumonitis 300,000 units procaine penicillin daliy	Uneventful recovery
Latter part of week wheezing became distressing	Aminophylline suppositories given, excellent response
On discharge (Feb. 9, 1951)	Child well. Neurological findings normal. Heart size normal. No evidence of cardiac failure. Uneventful recovery.

children, for about two hours, the rate was so rapid that it could not be counted; electrocardiograms were not recorded to identify the rhythm.

In the case of a 2½-year-old child reported by Gardner and associates,[3] of toxicity might have been due to the ephedrine, and the later occurring convulsions and gastrointestinal bleeding were due to the theophylline. The same authors also showed in mice that when ephedrine and theo-

phylline were combined, only one-half the lethal dose of ephedrine added to only one-third the lethal dose of theophylline caused death.

COMMENT

Ephedrine is a sympathomimetic drug. Its mode of action, in part by inhibiting the destruction of sympathin by amine oxidase,[4] results in increased sympathetic nervous activity. This appears as a pressor mechanism which causes the blood pressure to rise, the heart rate to increase, or both. To compensate for the rise in blood pressure, the heart rate may fall[5] as a direct result of stimulation of the aortic depressor reflex.

In our case, ephedrine was given in cumulative amounts which, in the end, may have been sufficient to fatigue the aortic depressor reflex, and to cause inadequate amounts of acetylcholine to be produced. The active sympathin or sympathin-like effects, no longer counterbalanced by the action of the acetylcholine breakdown, may have caused the development of the ectopic tachycardia.

That fatigue of the acetylcholine mechanism is the explanation for this untoward ephedrine effect is suggested by the failure of momentary stimulation of acetylcholine production by Prostigmin and vagal pressure to stop the tachycardia before the sustained vagal effects of digitalis were produced.

The sustained vagal effect is demonstrated by the wandering pacemaker and A-V nodal rhythm.[7]

The question naturally arises: Why was Mecholyl not used instead of digitalis? It would appear that Mecholyl, being a derivative of acetylcholine, should be the drug of choice when the failure of acetylcholine production is considered to be the cause for the tachycardia.

Unfortunately, the use of Mecholyl is frequently followed by serious side effects. Under the precarious conditions we dealt with it was feared that in the presence of peripheral collapse and low pulse pressure, any prolonged period of asystole which sometimes follows the administration of Mecholyl might adversely affect the chances for recovery.

The objections to quinidine were the stuporous state, low pulse pressure, heart failure, and wide ventricular complexes indicative of anoxia. The effect on the anoxic ventricular musculature by a high concentration of quinidine could not be predicted. Unless quinidine could quickly abolish the tachycardia, which is entirely unpredictable, the known toxic action of this drug on anoxic muscle (causing a drop in the already low pulse pressure) was the deciding factor against its use.

Intravenous procaine was not given because of the age of the child and the low pulse pressure. Procaine amide (Pronestyl) was not given because the tachycardia was not considered to be ventricular in origin, and because the pulse pressure was low and the liver was enlarged due to heart failure.

Though it might be argued that the widened ventricular complexes are more characteristic of ventricular than of supraventricular tachycardia, the appearance of the P waves between each of the ventricular complexes in lead aV_F and the presence of a ventricular rate of approximately 300 per minute point to a supraventricular ectopic focus.

Once convinced that the tachycardia was nodal or auricular in origin, the presence of a progressively enlarging liver, low pulse pressure, and presumably a low cardiac output made digitalis the drug of choice. We realized that if the tachycardia persisted, we would hardly expect to control the heart failure. Fortunately, the tachycardia was abolished by Cedilanid, potentiated by vagal stimulation.

There are numerous reports[9-17] in the literature on the beneficial use of digitalis preparations for paroxysmal supraventricular tachycardia, including a study of forty-one cases by Nadas and associates.[18] They state that "digitalis should be given an adequate trial in every case of supraventricular tachycardia and auricular flutter."

The beneficial effects of Cedilanid observed in our case are contrary to the experience with dogs reported by Seevers and Meek.[8] They report that "Amounts of digitalis preparations which did not in themselves alter cardiac rhythm greatly prolong the duration of arrhythmias produced by ephedrine."

SUMMARY AND CONCLUSIONS

A 2½-year-old asthmatic child was treated with repeated doses of ephedrine, theophylline, and phenobarbital until increased restlessness was observed. The heart rate rose to 300 per minute, signs of cardiac failure and peripheral collapse were observed, and the pulse pressure fell to 18 mm. of Hg.

An electrocardiogram showed a supraventricular focus for the tachycardia. Prostigmin, given after the application of carotid sinus pressure, did not abolish the tachycardia. Cedilanid (lanatoside C) was given intravenously in two doses of 0.3 and 0.2 mg. twenty minutes apart. Five minutes after the second dose had been given, the reapplication of eyeball pressure abolished the tachycardia.

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THE RELATIONSHIP OF BIRTH WEIGHT, THE SPEEDS OF OBJECT AND WORD PERCEPTION, AND VISUAL ACUITY

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ALTHOUGH it has been held that the handicapping effects of premature birth are largely overcome by the age of school entrance, studies have disclosed more neurological lesions, defective vision, slow speeds of visual perception, certain lateral dominance variations, and a higher incidence of reading failure among children of premature birth than in a nonpremature group.[1]

A comparison of 155 children who weighed 5.5 pounds or less at birth, with 439 children of comparable age, with birth weights over 5.5 pounds (considered as full term) disclosed a higher percentage of vision below 20/20 among the premature cases. They also presented a higher "average" (median) degree of subnormal vision at the ages from 5 through 9 years.[2]

Another study disclosed a positive correlation between birth weight and visual acuity among the premature children. Half of the group was composed of reading failures and the correlation among them was more than twice as great as that among the other half composed of nonfailures. The correlation among the premature reading failures was nearly five times greater than that among children of comparable age, also failing in reading and with birth weights over 5.5 pounds.[3]

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Positive relationship between measurements of the sharpness of vision, the degree of incorrect focus (refractive error), and the speed of perception was brought out in another study of unselected children between the ages of 6 and 17 years. Birth weights were not considered in the study, which is cited here as a forerunner of the investigation described in subsequent paragraphs.[4]

The present report is concerned with the correlation of birth weight and visual acuity with the speed of object and word perception. Object perception may be defined as seeing and recognizing objects. Word perception implies not only seeing the word but comprehending its meaning as well. Word perception involves brain areas 17, 18, and 19, as well as area 39 (Brodmann). The former subserves a visual but nonlanguage function, while the latter combines both a visual and a language function.

METHOD OF STUDY

A group of twenty-five pupils whose birth weights were less than 5.5 pounds (the premature group) was compared with a control group of equal number whose birth weights were 5.5 pounds or over. Visual acuity was measured by the Snellen method. The speeds of object and word perception were measured tachistoscopically by a method previously described.[5]

Pictures of familiar objects and word forms appropriate to the reading level of the pupils were projected in exposures of varied length on a screen the size of a primer page and in letters of a size comparable to that found in primary grade textbooks. This was done at the usual reading distance. Starting at 0.0033 second, the speed was gradually reduced until the child was just able to recognize and report what the picture or word was. A different word or picture was used for each test exposure. The maximum speed at which the child could observe and report pictures correctly was taken as the speed of object perception. Similarly, the highest speed at which he could report the word was taken as the speed of word perception.

The relationship of the various factors considered was determined by the statistical process known as correlation, which provides a coefficient of correspondence or coexistence of measurable traits, abilities, or characteristics. Coefficients of correlation may be positive, indicating some degree of relationship or parallelism, or negative, showing lack of correspondence. Perfect relationship is expressed as +1.00; complete inverse relationship as −1.00, different degrees being indicated by numerical values between these two points.

RESULTS

The present groups exhibited a low positive correlation between birth weight and the speed of object perception, with no difference between premature and full-term pupils in this respect. Although the correlation between birth weight and the speed of word perception was about the same among the controls, the premature group displayed a coefficient that was four times higher. The question of the effect of prematurity on word perception is suggested by these results. Does premature birth have more effect on the word recognition area in the brain (Brodmann 39) than on that of visual memory area (Brodmann 19)? The more recent phylogenetic acquisition of language would support this possibility.

A previous study of a different group had disclosed a low negative coefficient of correlation between birth weight and visual acuity among nonfailing pupils with birth weights over 5.5 pounds.[3] What little correspondence existed was inverse and of insignificant amount. The present control group exhibited the same tendency but with a larger negative value. On the other hand, the previous study showed a low positive correlation between the same factors in a premature group. The premature cases in the present investigation paralleled this but with a higher positive coefficient. Notwithstanding the different values in the two studies, the *differences* between control and premature group values were nearly the *same*.

The consistently negative character of the birth weight-visual acuity relationship among the controls and the consistently positive values among the premature cases suggested a possible relationship between visual acuity and the speeds of object and word perception as well as with birth weight and so this aspect of the matter was investigated.

One of the previous studies[4] had shown rather high positive correlative values between the speed of visual perception and visual acuity. While this is comparable to the speed of object

perception in the present study, no data were available to this investigator on the relationship of the speed of word perception to visual acuity. Results of an investigation of both of these relationships in the present groups disclosed positive correlations of both object and word perception speeds with visual acuity in both control and premature groups, the coefficient in the latter being higher than among the controls.

In view of the relationships disclosed, an attempt was made to demonstrate the interrelation of birth weight, visual acuity, and the speeds of object and word perception. Multiple correlations were calculated for each of the two types of perception under study. The results among control and premature groups disclosed moderate positive correlations for birth weight and visual acuity for each of the two perception speeds (object and word) among the controls, and considerably higher ones among the premature, being over three times greater for the speed of object perception and almost four times greater for the speed of word perception.

The study is limited by the small number of cases in the groups owing to the low incidence of prematurity and the difficulty of collecting such cases among children of school age. To the extent that these groups are representative, the following generalizations can be made.

Table I. Relationships

Factors	Coefficient of correlation			
	Birth weight 5.5 lb. or over	Probable error	Birth weight under 5.5 lb.	Probable error
Birth weight: speed of object perception	.11	.13	.11	.13
Birth weight: speed of word perception	.10	.13	.40	.12
Birth weight: visual acuity	−.23	.12	.36	.12
Visual acuity: speed of object perception	.60	.09	.76	.06
Visual acuity: speed of word perception	.34	.12	.60	.09
Birth weight: visual acuity: speed of object perception	.18	.13	.59	.09
Birth weight: visual acuity: speed word perception	.16	.13	.63	.08

SUMMARY

Birth weight, visual acuity, and the speeds of object and word perception tend to exhibit a higher correspondence in groups whose members weighed *less than 5.5 pounds* at birth. There is a tendency toward a lower positive relationship among those with birth weights of *5.5 pounds or over* as regard the speeds of object and word perception, visual acuity, and birth weight, but little if any real correspondence between birth weight and visual acuity is probable in this group. (Table I.)

Physicians, psychologists, and teachers may well consider the history of premature birth in cases involving language disabilities, *slowness* of object and word perception, and low visual acuity. If prematurity is an important handicap to learning, as the studies so far reported suggest, it poses a problem to pediatricians, ophthalmologists, and neurologists, in whose hands lie the amelioration of develop-

mental deficiencies. Psychologists and teachers, knowing a pupil to have weighed less than 5.5 pounds at birth, should bring the child to the attention of the physician for such treatment as he may deem wise, and at the same time make allowances for the presumed incapacity of the pupil to compete with others. It must be stated that there are individual differences in the response to prematurity just as there are in diseases, learning, and memory. Each child should be studied as an individual.

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The Dangers of Alcohol

June 16, 1736. A son of Daniel Drayton aged almost 9 years having drunk strong drink the night before (I think strong sweetened flip) after the north Windmill was raised was carried home in drink—vomited & was put to bed (but I think never spake more) seemed to sleep sound all night & in the morning fell into convulsions & died about ½ an hour before 12 of the clock.

FROM EASTHAMPTON, LONG ISLAND, RECORDS.

Philadelphia November 26, 1741. On the 11th of this Instant, a Child in this City about 3 or 4 Years of Age, died by drinking a large Quantity of Rum.

FROM BOSTON GAZETTE, Dec. 15, 1741.

THE TREATMENT OF TUBERCULOSIS OF THE SUPERFICIAL CERVICAL LYMPH NODES IN CHILDREN

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THERE appears to be considerable divergence of opinion as regard the optimal treatment of tuberculosis of the superficial cervical lymph nodes. There are several reasons for this. Before tuberculin testing of cows became general practice, tuberculous cervical adenitis was common. During this period, however, there was no satisfactory antituberculosis chemotherapy. Since that time, the disease has not been frequent enough for satisfactory appraisal of the newer therapeutic approach. This study, then, is an attempt to evaluate the various types of treatment with a suggestion as to the most practical one.

PATIENTS IN SERIES

Since 1947 there have been twenty-five proved cases of tuberculosis of the superficial cervical lymph nodes treated at the Medical College of Virginia Hospitals and twenty-one of these patients were admitted after Jan. 1, 1951. Seven of these were private patients and the other eighteen were admitted to the ward service. Some were admitted to the surgical service and others came directly to the pediatric wards; hence, there exists a great difference in approach to the problem.

DIAGNOSIS

Although tentative diagnosis can be made whenever a child, who reacts positively to the tuberculin test, has persistent enlargement of one or more of the superficial cervical lymph nodes, diagnosis was confirmed in all of the patients in this series by means of pathologic examination of the excised gland. Histologic findings were identical to those seen in tuberculosis.

RESULTS

It should be stated at the outset that all the patients reported in this series exhibited progressive enlargement and/or liquefaction of the superficial cervical lymph nodes. Those with equivocal involvement were treated expectantly and the results are not included in this group. The results of the various forms of therapy are summarized in Table I.

There was one death in this series (Case 15). This patient died after a blood transfusion while hospitalized following the excision of one glandular mass and awaiting surgery for others remaining. One child developed a fistula which later required surgical excision, and another developed tuberculous meningitis three months after excision of a tubercuous superficial cervical lymph gland and a six-week course of streptomycin therapy. She is now alive and well.

Excision of the involved node was effected in all the reported cases. On two occasions (Cases 14 and 21) incision and drainage was the initial surgical procedure, but later excision was

From the Department of Pediatrics, Medical College of Virginia, and the Pediatric Service, Medical College of Virginia, Hospital Division.

TABLE I

CASE	AGE	RACE	SEX	DURATION	SURGICAL TREATMENT OF NODE	ANTIMICROBIAL THERAPY	TONSILLECTOMY	COMMENT
1. A. B.	8 yr.	N	F	6 wk.	Excision	Streptomycin 1 mo. postop.	Yes No tbc	Uneventful
2. J. R.	10 yr.	N	M	4 wk.	Excision	Dihydrostreptomycin PAS } 2 da. preop. and 1 month postop.	No	Uneventful
3. L. C.	7 yr.	N	F	4 wk.	(1) Excision (2) Incision and drainage	None until wound began to drain 10 da. postop. Streptomycin 2 wk. postop. (2)	Yes No pathology report	Purulent drainage appeared 10 da. after excision of node. No medication before. Strep. 2 wk. postop. (2)
4. W. H.	3 yr.	N	M	1 mo.	Excision	INH 3 mo. postop.	No	Uneventful
5. S. S.	17 mo.	W	F	3 wk.	Excision	Strep. 1 wk. preop. Strep. 5 wk. postop.	No	Tbc meningitis 3 mo. later
6. E. L.	3 yr.	N	M	1 mo.	Excision	Strep. 8 wk. postop.	No	Uneventful
7. J. W.	5 yr.	N	M	4 mo.	Excision	Strep. 38 da. postop.	Yes No tbc	Uneventful
8. R. L. M.	6 yr.	N	F	1 yr.	Excision	Strep. 3 mo. postop.	Yes No pathology report	Phlyctenular conjunctivitis. Patient hospitalized later for swelling of other cervical nodes. Improved on strep. and PAS
9. S. W.	7 yr.	N	M	7 wk.	Excision	Strep. INH, PAS 7 wk. postop.	No	Moderately advanced pulmonary tbc
10. R. W. H.	2½ yr.	W	M	6-8 wk.	Excision	INH 1 mo. postop.	Yes No tbc	Uneventful
11. D. S.	5 yr.	W	M	10 wk.	Excision	None	Yes No tbc	Uneventful
12. J. E.	27 mo.	W	F	(1) 4 mo. (2) 2 mo.	(1) Excision (2) Excision	(1) INH and strep. 1 mo. preop. and INH 5 wk. postop. (2) INH 2 wk. preop. and 4 wk. postop.	Yes No tbc	2 yr. following excision of first node 3 more tbc nodes were excised
13. R. G.	2 yr.	W	F	6 wk.	Excision	INH 2 wk. preop. and 5 wk. postop.	No	Uneventful
14. E. L. O.	2 yr.	W	F	(1) 2 mo. (2) 5 mo.	(1) Incision and drainage (2) Excision	(1) Strep. 2 mo. postop. (2) Strep. 2 da. at time of operation	No	I. & D. gland with local instillation of strep. Gland became fluctuant 5 mo. later requiring excision

TABLE I—CONT'D

CASE	AGE	RACE	SEX	DURATION	SURGICAL TREATMENT OF NODE	ANTIMICROBIAL THERAPY	TONSILLECTOMY	COMMENT
15. M. M.	7 yr.	N	F	5 yr.	Excision	INH and strep. 7 da. preop. and 13 da. postop.	No	Widespread calcinosis neck, axillae, abdomen, etc. Death followed blood transfusion
16. J. T.	4 yr.	N	F	3 wk.	Excision	Strep. 9 da. postop. INH 1 wk. postop.*	No	Fistula postop.
17. S. M. W.	8 yr.	N	F	5 wk.	Excision	None	No	Uneventful
18. R. T.		N	F	1 wk.	Excision	None	No	Uneventful
19. F. C.	18 mo.	N	F	Since 18 mo. age. Increase in size 6 wk.	Excision	INH 4 wk. } preop. PAS 2 wk. } INH and PAS 6 wk. postop.	Yes	Uneventful
20. B. A.**	2½ yr.	W	M	4 mo.	Excision	Strep. 1 wk. postop. INH and PAS for 6 mo. postop.	No	Uneventful
21. L. M.***	5½ yr.	W	M	3 wk.	(1) Incision and drainage (2) Excision	(1) INH 1 mo. preop. (2) INH 2 mo. postop.	Yes No tbc	Wound drained for approx. 2 mo. after I. and D.
22. P. J.	3 yr.	N	M	3 mo.	Excision	Strep. 4 wk. } Preop. INH 6 wk. } Strep. 3 wk. } Postop. INH 6 wk. }	Yes No tbc	INH (1 mo.) failed to prevent drainage from node
23. R. L. R.	2 yr.	W	M	8 mo.	Excision	Strep. 10 da. postop. INH 3 wk. preop. INH 10 da. postop.	Yes Tbc	Uneventful
24. L. B.	17 mo.	N	F	1 mo.	Excision	Strep. and PAS 3 wk. preop. Strep. and PAS 4 wk. postop. INH 8 wk. postop.	Yes No tbc	Node ruptured and drained 2 wk. preop. Some drainage postop. Slight weakness of mandibular branch facial nerve
25. J. R.	2 yr.	N	M	2 mo.	Excision	INH 3 wk. } PAS 2 wk. } INH 4 wk. } PAS 4 wk. }	Yes No tbc	Uneventful

*Medication prescribed for one month but apparently was not taken.
**Private patient of Dr. Albert M. Edmonds.
***Private patient of Dr. Walter Bundy.

necessary. In another instance (Case 3) purulent drainage appeared ten days following excision of the node and necessitated incision and drainage. A second excision was required in one case by the progressive enlargement and fluctuation of three more superficial cervical lymph nodes two years following the first operation.

Isoniazid (INH) was used alone or in combination with other drugs in fourteen cases. Attempted conservative treatment with isoniazid for one month failed in two instances. Once purulent drainage appeared spontaneously and on the other occasion liquefaction was so complete that incision and drainage was necessary before later excision could be effected.

Streptomycin or dihydrostreptomycin was used alone or in combination with other drugs in sixteen patients. As noted above, successfully treated tuberculous meningitis occurred in one case. In another, streptomycin for two months following incision and drainage of a tuberculous cervical lymph node failed to promote healing and excision was necessary five months after the first surgical procedure.

No antimicrobial therapy accompanied surgical excision of the affected node in four cases. Three of these healed uneventfully, but purulent drainage appeared from the other ten days following excision. A two-week course of streptomycin was initiated at that time with satisfactory results.

CASE REPORT

M. M., a 7-year-old Negro female, was well until 9 months of age. At that time she developed anorexia, fever, and general malaise and was never in good health thereafter. When she was about 2 years of age, marked swelling appeared on each side of the neck, and there was discharge from the left eye. It is said that she received some streptomycin therapy.

In March, 1954, she was hospitalized at Dooley Hospital for diagnosis. Excision biopsy of an axillary node substantiated previous impression of tuberculosis. On June 3, 1954, she was readmitted to Dooley Hospital for excision of the massive cervical lymphadenopathy. Physical examination at that time revealed a frail Negro female with masses the size of a large orange in both anterior cervical areas and opacity of the left cornea (Fig. 1).

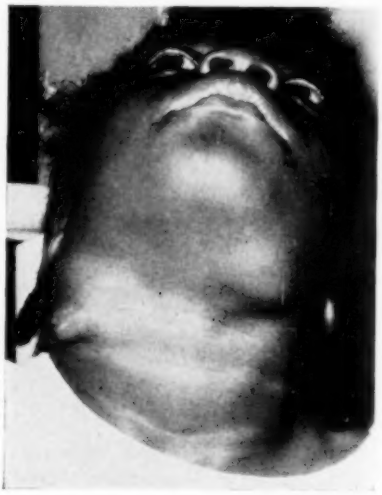

Fig. 1.—Massive cervical lymphadenopathy.

X-rays revealed marked calcinosis in the soft tissue of the neck (Fig. 2), large calcific nodes in the left hilum (Fig. 3), calcium deposits in the left axilla (Fig. 4), and many areas of calcification in the abdomen (Fig. 5).

Therapy with isoniazid and streptomycin was instituted on admission, and one week later the large right cervical mass was surgically excised without difficulty.

Thirteen days following operation (June 23, 1954) the patient's hemoglobin was 8.5 grams. In order to satisfactorily prepare her for further

surgery she was transfused with 300 c.c. blood. Fifty minutes after the procedure, the patient developed a chill and fever. She was treated with Benadryl and acetylsalicylic acid, but died a few hours later. Urinalysis was negative. The blood was completely restudied, but no cause for the reaction could be determined. No autopsy was obtained.

Fig. 2.—Calcinosis in soft tissue of neck (cervical glands).

Fig. 3.—Large calcific nodes of left hilum.

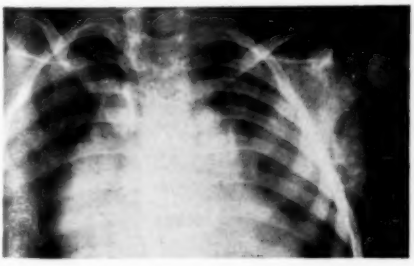

Fig. 4.—Calcium deposits in left axilla.

DISCUSSION

As mentioned earlier, there are many different opinions as to the best method of therapy of tuberculosis of the superficial cervical lymph glands. Part of the problem stems from the difference in opinion as to pathogenesis. One opinion is that the majority of cases occur as a result of primary tuberculous infection in the tonsils or adenoid tissue, with drainage to the regional lymph nodes.[1] Others feel that tuberculous cervical adenitis is more often the result of hematogenous dissemination of tubercle bacilli.[2] It seems likely that either can be and is the mode of infection in some in-

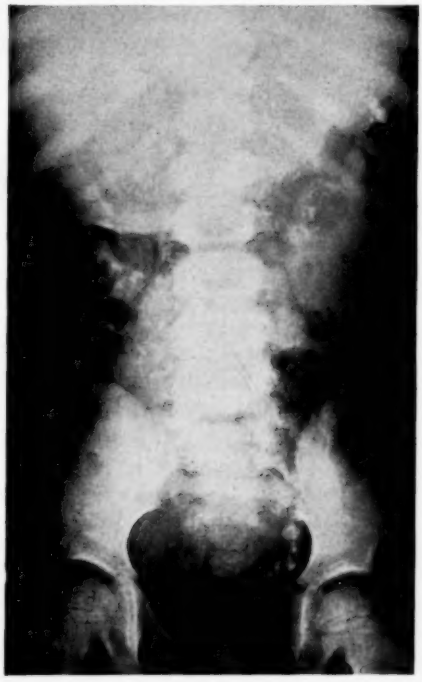

Fig. 5.—Calcific densities in abdomen.

stances, but belief in one of these two theories obviously necessitates some difference in therapeutic approach. If one adheres to the belief that tuberculous cervical adenitis is part of the so-called primary complex, tonsillectomy and adenoidectomy is indicated. Swenson and Small,[3] for example, advise tonsillectomy and adenoidectomy. If the enlarged glands do not recede, they advise excision.

Belief that the glandular involvement is part of hematogenous spread allows for a different approach. In such case, removal of tonsils must be decided on the usual basis of history of previous infections and physical appearance of the tonsils themselves.

Of the thirteen patients in this series who had tonsillectomy, eleven had satisfactory pathologic examination of the removed tissue. No microscopic section was studied in the other two instances. Of the eleven specimens studied, only one showed a lesion compatible with tuberculosis. The others showed only chronic inflammation. Whether or not this is significant is debatable. Actually, the primary tuberculous lesion is most often minute and it may well be that the lesion was not observed when the specimen was sectioned for microscopic study. However, the fact remains that in this series there is little evidence that the tonsils were the portal of entry of the tuberculous infection.

Whether or not the involved nodes should be excised or widely incised with local use of streptokinase and streptodornase poses another question. We have had no experience with the latter. In two private cases in this series, node incision, without use of enzymes, was done. The results were not satisfactory. Drainage continued for approximately two months in one instance and purulent drainage appeared from the wound five months later in the other. Hazlehurst[4] has recently reported the use of streptokinase and streptodornase in the treatment of eleven patients (seventeen suppurative nodes). One of his patients required ten weeks and another nine weeks before healing took place. Whenever the involved gland is widely incised, drainage continues for a varying period of time and during that period the danger of spread of tuberculous infection is constant. Our experience with excision has been most satisfactory. Even in two instances when liquefaction had occurred, excision followed a short period of antimicrobial therapy with a good result. In none of the patients reported was antimicrobial therapy effective in preventing progressive enlargement, caseation, or liquefaction. On the other hand, use of the antimicrobial agents immediately before and after excision of the gland has been satisfactory. It would appear that isoniazid is preferable to streptomycin in this regard. One patient developed tuberculous meningitis three months after surgical excision of a tuberculous node and she received streptomycin therapy for one week before operation and five weeks afterward. So far there has been no report of tuberculous meningitis which developed after a patient had been given isoniazid therapy for a period of one week or longer.

It has been our impression that progression of tuberculous disease in the superficial cervical lymph nodes in children is often sudden and is usually more rapid than that seen in adults. Certain differences in therapy would therefore, seem indicated.

In view of the foregoing, it is our feeling that progressive tuberculosis of the superficial cervical lymph nodes in children should be treated in the following manner: Complete excision of the node or nodes and the additional use of isoniazid and PAS therapy for at least one month preoperatively and for a two- to three-month period of time after surgery would appear to be the ideal approach to the problem. In this manner, an accessible focus of tuberculosis can be readily eradicated and any active tuberculous process may have a reasonable course of antimicrobial therapy.

While it may well be true that the primary tuberculous focus is not present in the tonsils or adenoids in this condition, it is also true that an attack of tonsillitis may cause activity of the tuberculous process in the regional lymph node. Whenever there is the slightest question of tonsillar disease, therefore, tonsillectomy and adenoidectomy is indicated.

If purulent drainage from the nodes is already present or if the area of liquefaction is so large that satisfactory excision of the area cannot be effected, incision and drainage, with local use of streptokinase and streptodornase after the manner advocated by Hazlehurst, appears to be indicated. Even in this instance, however, later excision of the area would seem wise. Further, isoniazid and PAS therapy for several months during and after the healing process appears to be indicated.

SUMMARY

The results of various types of treatment in twenty-five cases of tuberculosis of the superficial cervical lymph nodes in children are reported. A suggested method of therapy is outlined.

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THE NEW YORK CITY CONSULTATION SERVICE FOR ORTHOPEDICALLY HANDICAPPED CHILDREN

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MANY crippled children's programs provide diagnostic and consultation service clinics for handicapped children—orthopedic, rheumatic fever and cardiac, hearing, epilepsy, cleft palate, eye, etc. In some instances, these services have been provided directly by the Crippled Children's Agency; in other instances, they have been purchased by the Crippled Children's Agency from hospitals in the community, usually the teaching hospitals affiliated with medical schools. In either method, the purpose has been to provide the mechanism whereby physicians and families in the community may secure a careful evaluation of a child suspected of having a handicap, without charge to the family. Such a community service usually does not provide treatment itself, but should be a device to lend diagnostic support to the case-finding agencies in the community, and to make immediate referral to the community's treatment and rehabilitation services. It is not designed to compete with hospital services or private physicians, but rather to offer a means of early case finding and diagnosis within the framework of a crippled children's program for those unable to afford private care.

Until December, 1952, the Bureau for Handicapped Children of the New York City Department of Health operated one diagnostic and consultation service clinic for orthopedically handicapped children in one of the district health centers of the Health Department. It was felt that the physical location of the service in a health center presented several disadvantages in patient care: (1) the lack of some essential diagnostic tools such as x-rays, laboratory service, etc.; (2) the fact that the service was a detached one, not linked up with a recognized treatment agency. For this reason, in December, 1952, the orthopedic consultation service clinic was moved from the health center to a teaching hospital; the director of the teaching hospital assigned one of the young hospital staff orthopedic surgeons to the staff of the orthopedic consultation service. In addition to the orthopedic surgeon assigned by the teaching hospital, the staff consists of a public health nurse and a clerk provided by the Department of Health. Children are seen only once.

This report will present data on the operation of the orthopedic consultation service clinic from July 1, 1954, to Jan. 1, 1955, and will answer certain basic questions:

1. What are the costs of operating such a consultation service?
2. What are the clinical findings in a group of children seen in such a consultation service?

From the Bureau for Handicapped Children, New York City Department of Health, and the Hospital for Special Surgery, Philip D. Wilson, Director.

3. What are some of the administrative lessons to be learned?

COSTS

During the six-month period from July 1, 1954, to Jan. 1, 1955, 131 children were seen in the orthopedic consultation service clinic, which meets three hours each week. A total of $460.85 was expended directly by the Department of Health, or an average of $3.52 per child. The largest single item of service provided in terms of cost is the orthopedist's service which comprises 61 per cent of the total funds expended (Table I).

TABLE I. COSTS OF OPERATING ORTHOPEDIC CONSULTATION SERVICE CLINIC, JULY 1, 1954, TO JAN. 1, 1955

ITEM OF SERVICE	COST
Orthopedist's service	$280.20*
Public health nursing service	101.47†
Clerical service	79.18‡
Total	$460.85

*For 24 sessions at $11.675 per session.
†For 55¾ hours at $1.82 per hour.
‡For 53½ hours at $1.48 per hour.

These data on costs do not include such indirect items such as use of space, heating, lighting, depreciation of equipment, and the occasional use of x-rays and laboratory service as indicated for an individual child. All of these facilities are provided by the hospital as a community service.

CLINICAL FINDINGS

The diagnoses of the children seen in the consultation service clinic for a six-month period are shown in Table II. The largest single individual diagnoses of the children seen are scoliosis, postpoliomyelitis paralysis, flatfeet, cerebral palsy, lordosis, and round back; scoliosis was found in one-third of the children seen by the service.

Diagnostic categories included "unknown or uncertain causes" (60.3 per cent); "prenatal influences and injuries associated with birth" (13.8 per cent); "infections" (5.3 per cent); "trauma or physical agents" (3.8 per cent); "new growths" (0.8 per cent). No orthopedic deformity was found in 5.3 per cent of the children. (Table II.)

TABLE II. DIAGNOSES OF CHILDREN SEEN IN ORTHOPEDIC CONSULTATION SERVICE CLINIC, JULY 1, 1954, TO JAN. 1, 1955

DIAGNOSIS		NO. CHILDREN	PER CENT
I. Prenatal influences and injuries associated with birth		18	13.8
Cerebral palsy	4		
Other*	14		
II. Infections		7	5.3
Postpolio paralysis	7		
III. Trauma or physical agents		5	3.8
Post-traumatic deformities of bone and joints			
IV. New growths		1	0.8
V. Unknown or uncertain causes		79	60.3
Scoliosis	46		
Flatfeet	5		
Lordosis	4		
Round back	4		
Osgood-Schlatter's	3		
Muscular dystrophy	2		
Round back, flatfeet	2		
Other*	13		
VI. No orthopedic deformity		7	5.3
VII. No information		14	10.7
Total		131	100.0

*Composed of one case each of a wide variety of orthopedic conditions.

Of the 131 children seen, ninety-three children (71 per cent) were referred for further orthopedic care and rehabilitation; of this group, eighty-eight children elected referral to a hospital clinic and five children to a private physician. No orthopedic treatment was deemed necessary in thirty-eight children (29 per cent).

Of the 131 children seen, ninety-three (73 per cent) were recommended

for placement in regular classes within the public school system, and five children (4 per cent) were recommended for home instruction. Thirty children (23 per cent) were of pre- or post-school age in which school placement would not be applicable. These data on school placement are considerably different from the data on city-wide school placement activities conducted by the Bureau for Handicapped Children. The essential differences are that the orthopedic consultation service clinic recommended a higher percentage for regular classes in public schools, a lower percentage for home instruction, none for orthopedic or cerebral palsy classes in public schools, and none for transportation and elevator passes in public schools (Table III).

TABLE III. EDUCATIONAL PLACEMENT RECOMMENDED FOR CHILDREN, JULY 1, 1954, TO JAN. 1, 1955

PLACEMENT RECOMMENDED	OCS* CLINIC		CITY-WIDE BY BHC†	
	NO.	PER CENT	NO.	PER CENT
Regular class	96	73.3	1,347	56.4
Orthopedic class			342	14.3
Cerebral palsy class			24	1.0
Home instruction	5	3.8	558	23.4
Transportation and elevator pass			118	4.9
Hospital or convalescent care				
Not applicable‡	30	22.9		
Total	131	100.0	2,389	100.0

*Orthopedic consultation service clinic.
†Bureau for Handicapped Children.
‡Children were of pre- or post-school age.

ADMINISTRATION

During the six-month period July 1, 1954, to Jan. 1, 1955, appointments had been made for a total of 194 children at the orthopedic consultation service clinic; 131 children (67.5 per cent) were actually seen in the service. In other words, 32.5 per cent of the children referred failed to keep their appointments. The reasons for the broken appointments are unknown. The referring agency was notified of each such child who failed to keep his appointment, as a means of follow-up of broken appointments.

Sources of referral of children to the orthopedic consultation service clinic also provide leads in the administration of the service (Table IV). A total of 113 children (86.2 per cent) were of school age referred by working paper clinics and the school health service of the Department of Health. Only ten children (7.7 per cent) were of infant and preschool age referred by the child health stations of the Department of Health. No children were referred by private physicians.

TABLE IV. SOURCES OF REFERRAL OF CHILDREN TO ORTHOPEDIC CONSULTATION SERVICE, JULY 1, 1954, TO JAN. 1, 1955

SOURCE	NO. CHILDREN	PER CENT
Working paper clinics	67	51.1
School health service	46	35.1
Child health stations	10	7.7
Bureau for Handicapped Children	5	3.8
Other	3	2.3
Total	131	100.0

DISCUSSION

The fact that at least 84 per cent of the children seen had an orthopedic condition and that 71 per cent of the children seen were referred for orthopedic care and rehabilitation would amply justify the need for the orthopedic consultation service. Even the fact that 16 per cent of the children seen did not have an orthopedic condition has a positive value to the child and to the referring physician in the Health Department services. These facts should be correlated with the relatively low direct cost ($3.52 per

child) to the Health Department for the operation of the consultation service.

The values of maintenance of such a service in a teaching hospital have briefly been commented upon previously, namely, the opportunity for providing expert consultation and all of the diagnostic work-up necessary, as well as the maintenance of some degree of continuity of care through referral to a hospital orthopedic service of high quality. Furthermore, the fact that the director of the hospital service assigned one of his own younger staff members to the consultation service has assured a high caliber of orthopedic diagnostic work. The values to a teaching hospital of locating a consultation service within the hospital are: (1) a supply of a wide variety of diagnoses for a young orthopedist; (2) a supply of a wide variety of diagnoses to the orthopedic service of the hospital for teaching purposes. With the decline in the incidence of orthopedically handicapping conditions in children, because of the decrease in disability due to osteomyelitis, rickets, and tuberculosis of bone and joint, maintenance of an adequate caseload in hospitals approved for residency training in orthopedic surgery has become a serious problem in an urban area such as New York City. The location of an orthopedic consultation service in a leading hospital therefore is of value to the hospital in supplying children with orthopedic handicaps for staff training.

A possibly significant finding is the fact that 13.8 per cent of the children seen in the consultation service had an orthopedic diagnostic condition classified as due to prenatal influences and injuries associated with birth, while only 7.7 per cent of the children seen were infants and preschoolers referred by the Health Department's child health stations. This reflects the larger problem of delay in early case finding of orthopedically handicapped children. Analyses of orthopedically handicapped children reported to the city-wide register maintained by the Bureau for Handicapped Children and of orthopedically handicapped children cared for under the state-aid medical rehabilitation (payment) program have previously pointed up the need for earlier case finding. It is possible that, with improved undergraduate and graduate medical education and with the inclusion of more pediatricians in the care of orthopedically handicapped children, case finding might be improved. The consulting orthopedic surgeon to the Department of Health now regularly participates in the preservice training of child health physicians, with special emphasis on the early diagnosis of orthopedic disabilities, in the hope that it will stimulate early case finding.

Only 3.8 per cent of the children seen in the consultation service had an orthopedic diagnosis classified as due to trauma or other physical agents. If this sample of children is a representative one, it would appear that, while accidents have become a prominent cause of mortality in children and youth, they play a relatively small role in disability among children and youth.

Most of the school-aged children seen in the consultation service were recommended for placement in regular classes within the public school system, in contrast to the city-wide school placement data of the Bureau for

Handicapped Children previously mentioned. Possible explanations for the differences are: (1) there may be a real difference in the degree of handicap between the children seen in the orthopedic consultation service and those children in the city-wide school placement activities; (2) personal examination and evaluation of the children, as opposed to paper review of applications, is the only sound medical way of conducting a school placement program. This latter explanation is supported by the findings of two special studies conducted by the Bureau for Handicapped Children in which it was found that one-third of the children examined in orthopedic classes in public schools were found able to be placed in regular classes, and that one-half of the orthopedically handicapped children on home instruction were found able to attend school.

It is significant that 32.5 per cent of the children referred to the consultation service did not keep their appointments. Since the reasons for such broken appointments are unknown at present, a special study of this aspect of the consultation service is indicated.

Two essential professional disciplines are lacking in the orthopedic consultation service at the present time—the pediatrician and the medical social worker. It is hoped that steps may be taken in the near future to provide these services.

SUMMARY

This report describes a consultation service maintained by the official health agency in New York City for orthopedically handicapped children, operated in conjunction with a teaching hospital. Significant findings are as follows:

1. The direct cost to the official health agency is $3.52 per child seen.
2. At least 84 per cent of the children seen had an orthopedic condition, and 71 per cent had an orthopedic condition warranting further orthopedic care and rehabilitation.
3. Seventy-three per cent of the children seen were recommended for placement in regular classes within the public school system.
4. One-third of the children referred to the consultation service failed to keep their appointments.
5. Only 8 per cent of the children referred were infants and preschoolers referred by child health stations of the Department of Health.

The implications of these findings are discussed from the viewpoint of improvement of services to orthopedically handicapped children.

PHOTOGENIC EPILEPSY

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SEIZURE discharges in the electroencephalogram as a result of intermittent photic activation have often been reported in the literature.[1-5] These may, in some instances, be associated with attacks of grand mal, petit mal, myoclonic jerks, or a combination of these.[6] Also recorded from time to time are instances of spontaneous or induced clinical seizures following exposure to intermittent light encountered in everyday life.[7-12] Bickford and associates,[10] in a study of twenty-seven cases, classified them into three groups: (a) a clinically sensitive group in whom manifest attacks were induced by light intensity encountered in daily life, (b) a less sensitive group in whom clinical attacks were possible only in the laboratory with high intensity illumination, and (c) a still less sensitive group in whom no clinical seizures could be produced, but an abnormal discharge obtained on the electroencephalogram after exposure to high intensity light. More unusual were those patients[10, 11] who indulged in regular self-precipitation of the attacks, thus apparently deriving some satisfaction or pleasurable sensation.

It has been stated[10, 12, 13] that some patients are particularly sensitive to the red end of the spectrum. This communication is concerned with an investigation of the relative effectiveness of different parts of the visible spectrum in precipitating seizures in children. Some of the problems associated with an investigation of this kind have been reviewed by Carterette and Symmes.[13]

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*Colombo Plan Fellow, sponsored by the Dominion Government of Canada.

CASE REPORTS

Case 1.—R. T., a 13-year-old girl, began having occasional generalized seizures at the age of 10 years. At 11, she began to have myoclonic jerks of her arms and head. These were particularly liable to occur during the first hour after waking in the morning, and while out of doors, especially in bright light.

On examination, she was an intelligent, attractive child in good general health. There were no abnormal signs in her central nervous system.

The electroencephalogram showed spontaneous bursts of bilaterally synchronous atypical spike and wave activity. Photic stimulation regularly precipitated myoclonic jerks of her head, and these attacks were accompanied by spike and wave activity in the electroencephalogram similar to the spontaneous discharges (Fig. 1).

Case 2.—C. M., a 6-year-old girl, began to have, at the age of 10 months, attacks characterized by blinking and sudden jerking of the head and arms. At 2 years, the attacks became more frequent until she was having about fifty a day. Some of the attacks were severe enough to throw her down, although the child never had a generalized seizure.

The mother noticed that the attacks were more frequent in bright light, particularly when the child went out of doors into bright sun or the glare of snow. The response to anticonvulsant medication was poor.

The only significant finding on clinical examination was a convergent concomitant strabismus of about 15 degrees. Laboratory investigations were negative except for the electroencephalogram which showed occasional spontaneous bursts of bilaterally synchronous atypical spike and wave activity. The spike and wave activity accompanied by myoclonic jerks of the head and arms could also be induced by stroboscopic activation (Fig. 1).

CASE 3.—J. P., a 10-year-old girl of "dull normal" intelligence, began to have episodes of petit mal, characterized by short periods of unconsciousness associated with staring, blinking, and occasionally rhythmical jerking of both arms, at the age of one year. At the age of 3, she had a generalized nocturnal seizure lasting about fifteen minutes. At the age of 8, she had a second generalized seizure while watching a television set that was flickering badly. At the time of investigation she was having fifteen to twenty minor attacks a day, mostly associated with sudden changes in intensity of light. Anticonvulsant therapy was of no clinical benefit.

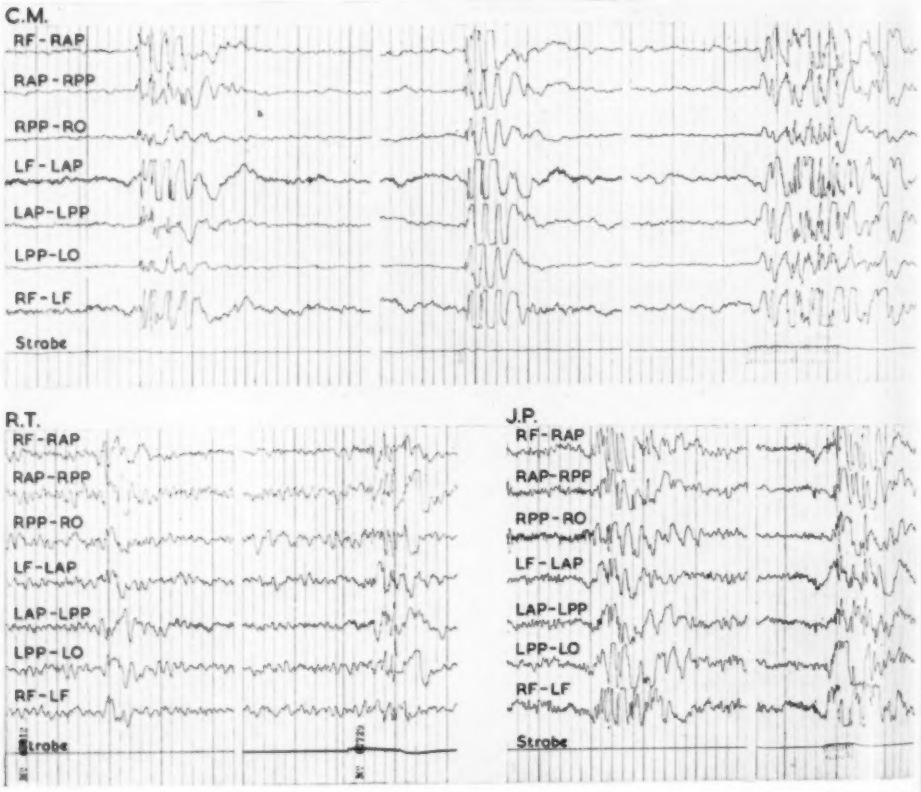

Fig. 1.

Examination revealed an obese girl in good general health with no abnormalities in her central nervous system.

The only significant laboratory investigation was the electroencephalogram which showed spontaneous bursts of bilaterally synchronous atypical spike and wave activity which could be precipitated by stroboscopic activation (Fig. 1).

CASE 4.—E. S., an 8-year-old girl began, at the age of 6, to have episodes in which she would wave her outstretched fingers backward and forward across her eyes. Her mother noticed that during these episodes she would "look blank," and give slight rhythmical jerks of her head, shoulders, and arms. The whole incident lasted about ten seconds. She did this about twenty times each day. When asked why she did it, the reply was that she did not know, but she liked doing it. The mother also noticed that when the child went from shade into bright light, she would have a jerk or a series of jerks. In addition, she had two nocturnal grand mal seizures during the previous six months.

On examination she was a cooperative, intelligent child, with no apparent clinical abnormality. Episodes of unconsciousness associated with slight myoclonic jerks of the upper half of the body could be induced by flickering light. The electroencephalogram revealed spontaneous bursts of spike and wave activity. Similar bursts associated with clinical attacks could be induced by stroboscopic activation.

TECHNIQUE

Electroencephalograms were carried out using a Grass eight-channel machine and bipolar recording from silver scalp electrodes. Sensitivity to interrupted light was tested by means of a stroboscope, using "Sylvania" type SA 309 Strobotron bulb and a flash rate of 15 per second. In each case the distance between the patient and the source of light was so adjusted that the onset of flash on the stroboscope consistently produced an almost immediate seizure discharge in the patient. This varied from 28 to 32 inches, and was kept constant in each patient. To reduce the possibility of an adaptation to flashes a minimum interval of 20 seconds was allowed to lapse between each burst of flashes.

At the time of recording, the patient was lying down on a stretcher in a quiet room under subdued general illumination. The pupils were dilated and fixed by atropinization. Particular care was taken to see that the child's eyes were kept open and directed toward the source of light during the stroboscopic stimulation.

To determine whether these children were sensitive to a particular wave band of the spectrum, effects of three Kodak Wratten filters, red, green, and blue (Nos. 24, 58, and 44A), were studied. Special light-tight goggles were used with identical filters screwed on to them in front of each eye. Each filter was used at least twice in random order on each patient.

The use of these filters resulted in a considerable reduction in the intensity of light at the eye, and it was therefore necessary to reduce the intensity of the white light in order that a true comparison might be made. This was achieved by placing a suitable thickness of opaque white paper in front of the eyes. The values of probable light intensitiy at the eye were compared by using the stroboscope at 36 inches from a Weston Photronic cell. Approximately the same intensity (about 20 per cent of the incident light) was obtained with the opaque paper, blue and green filters, but about 36 per cent with the red filter, because of some excess of red in the source of light.

Apart from occasional resistance from J. P., the children cooperated well.

RESULTS

With the patients at rest, the electroencephalogram showed occasional bursts of atypical spike and wave. In all four children exposure to a flickering light produced similar seizure discharges in the electroencephalogram associated with clinical seizures characterized by myoclonic jerks in the face and upper extremities.

Table I compares the results obtained with color filters and opaque white paper. The results were expressed in terms of the presence or absence of seizure discharges on the electroencephalogram, during two-second photic stimulation.

TABLE I

NAME		RED FILTER	GREEN FILTER	BLUE FILTER	OPAQUE PAPER
R. T.	(a)	6	1	2	12
	(b)	4	8	8	0
C. M.	(a)	9	9	5	1
	(b)	3	3	6	10
J. P.	(a)	3	0	2	1
	(b)	9	7	7	7
E. S.	(a)	17	12	5	0
	(b)	0	0	4	21

(a) Number of instances with no seizure discharge on the electroencephalogram during two-second exposure to intermittent light stimulus.

(b) Number of instances with seizure discharges on the electroencephalogram during two-second exposure to intermittent light stimulus.

As can be seen, general reduction in the intensity of light protected R. T. from attacks, whereas the color filters had little effect. E. S. was protected by red and green filters. C. M. derived some benefit from red and green filters. J. P.'s seizures were relatively unaffected by any measure.

There was considerable variability of response. In all four patients a seizure discharge would, on some occasions, result from a single flash or a pair of flashes, whereas twenty seconds later there would be no response to a burst of flashes lasting four seconds or longer. In both instances the experimental conditions were apparently identical. It is suggested that the patients are able to inhibit, to some extent, the seizure discharges in the same way that some epilepties can inhibit a seizure during its initial stages.

DISCUSSION

Photogenic epilepsy is not uncommon. In many, as in the cases reported here, ordinary daily light conditions produce innumerable seizures. Anticonvulsant medication was of little value in these cases, and this is the general rule.

It has been reported[10, 12, 13] that some of the patients were particularly sensitive to the red end of the spectrum. This was not observed in our cases. However, it does appear from the results and from the results of previous authors that patients do vary in their sensitivity to different parts of the visible spectrum. Consequently suitable colored spectacles can be used to diminish the number of seizures. Probably the best way to arrive at the

most suitable color of glasses for a particular patient is to do an electroencephalogram, using photic stimulation with white light, and the "primary colors"—red, green, and blue—each of comparable intensity. It is then possible to see if the patient had more protection with any one filter or whether a general reduction in light intensity is necessary. It is interesting to note that red and green glasses afforded almost complete clinical relief to C. M. and E. S. The other two were benefited most by smoked glasses.

CONCLUSION

1. Four clinically sensitive cases of photogenic epilepsy are reported. One of these had self-induced attacks.

2. No particular sensitivity to a band in the visible spectrum was found common to all four.

3. It is suggested that patients with photogenic epilepsy have an electroencephalogram, using photic stimulation with white and colored lights so that their relative sensitivity may be determined. Suitable colored glasses can then be prescribed.

We wish to thank Prof. R. Richmond of the Light Laboratories, University of Toronto, for his invaluable help.

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OXALOSIS WITH RENAL CALCINOSIS DUE TO CALCIUM OXALATE

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THE literature on urinary tract lithiasis is voluminous. The etiology, incidence, distribution, and chemical composition of the calculi have been discussed time and again and are not the subject of this paper. However, reports on oxalosis and studies of oxalate metabolism are rare, the last comprehensive report being that of Jeghers and Murphy[1] in 1945. For that reason and because of the unusual history, clinical and autopsy findings, a case of renal failure from renal lithiasis due to calcium oxalate is reported.

CASE REPORT

J. R. L., a white male child, 4 years 8 months of age, was admitted to the Children's Hospital of Pittsburgh on Aug. 15, 1953, and died on Aug. 30, 1953. The chief complaint on admission was "swelling of the face" of one week's duration. The family history revealed that a maternal aunt had a right nephrectomy in 1953 at age 52. The diagnosis was hydronephrosis and recent subcapsular hemorrhage. No renal stone was found. A maternal uncle, age unknown, had displayed a typical history of renal stone colic and in 1947 his right kidney was removed. The diagnosis was hydronephrosis with abscess formation. No stone was found. Another maternal uncle, age 54, had a history of recurrent pyelitis which responded to conservative therapy. No stone was ever found. A maternal cousin had a left nephrectomy at age 17 because of pyelonephritis. The diagnosis was torsion of the left kidney with abscess formation. No stone was found. The patient had eight siblings living and well and two dead, causes unknown.

The birth history and neonatal history were not remarkable. The past medical history was not significant except as it related to the present illness. The patient's first symptoms of urinary tract difficulty occurred at 15 months of age, at which time the mother noticed that the infant grunted and cried when urinating. Shortly thereafter the patient passed his first stone accompanied by severe pain. When the child was 2 years 8 months old, severe abdominal pain developed and an operation was performed. Four stones were removed from the right ureter. There was no subsequent therapy until he was 4 years 4 months old. (Approximately nine stones were passed during this interval.) At this time, in March, 1953, an operation for removal of stones in the bladder and left ureter was performed. A blood urea nitrogen at this time was 15 mg. per cent. The patient did poorly following the operation. He was sent home on a low calcium diet. Secondary anemia was treated with liver, iron, and vitamin B_{12} without favorable response. The child passed only one stone from March, 1953, until his admission to the Children's Hospital of Pittsburgh. However, his appetite was poor, he was listless, and for two months before admission to another hospital on Aug. 3, 1953, he had morning nausea with vomiting two days

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out of every three. He was finally hospitalized elsewhere, twelve days before admission to this hospital, because of headache and pain in the back in addition to the other complaints enumerated. During his stay in that hospital he received 1,000 ml. of whole blood and was digitalized when signs of right-sided heart failure developed (Aug. 10, 1953). Laboratory findings showed anemia, pus in the urine (for which he received Aureomycin), blood calcium of 6.2 mg. per cent, and blood phosphorus of 10.3 mg. per cent. The blood urea nitrogen was 9 mg. per cent on admission and rose to 150 mg. per cent on the day before transfer to the Children's Hospital of Pittsburgh. Facial edema occurred one week before the transfer and edema of the legs developed shortly thereafter. Urinary output was stated to be diminished at this time. Intravenous pyelogram was reported as showing no function at six hours.

Physical Examination.—Physical examination on admission revealed: temperature 97.4° F., pulse 94, respirations 18, blood pressure 150/106, weight 35 pounds 4 ounces (16 kilograms). Positive physical findings were edema of the face, especially supraorbital, edema of the lower legs, cardiac enlargement, and scars of previous operations. A roentgenogram of the chest showed cardiac enlargement. A plain film of the abdomen revealed calculi in the bladder and diffuse calcification outlining the kidney parenchyma bilaterally (Fig. 1).

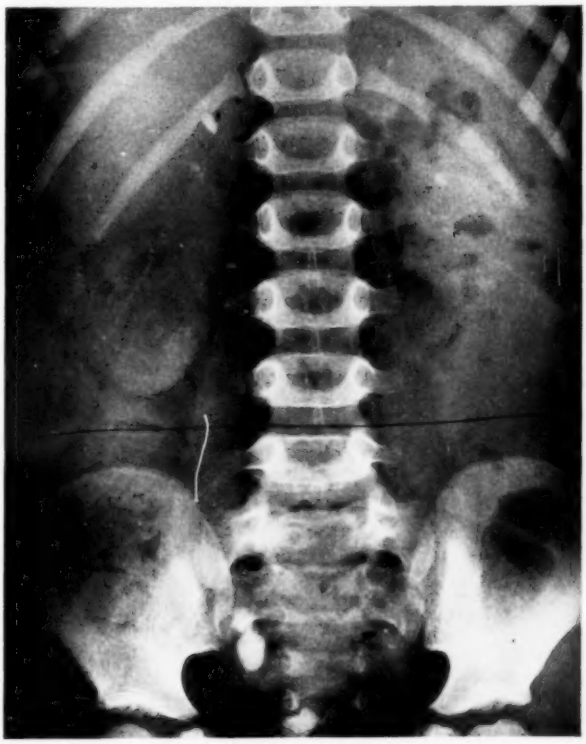

Fig. 1.—Roentgenogram of the abdomen and pelvis showing calculus in the urinary bladder and diffuse calcification in kidney parenchyma.

Urinalysis revealed many pus cells in addition to the 4 plus albuminuria. The hemogram showed an erythrocyte count 4,010,000; hemoglobin 11.6 grams; total leukocytes 9,900 with 70 per cent polymorphonuclears, 3 per cent myelocytes, 20 per cent lymphocytes, 7 per cent eosinophils. The corrected sedimentation rate was 4 mm. in one hour and the hematocrit was 30 per cent. Blood chemistries showed Co_2 5.5 meq. per liter, chloride 103 meq. per liter, sodium 150 meq. per liter, potassium 7.6 meq. per liter, phosphorus 16.9 mg. per cent, nonprotein nitrogen 297 mg. per cent, sugar 123 mg. per cent, total protein 6.25 grams per cent with albumin 3.62 grams and globulin 2.63 grams. Blood calcium was 6.5 mg. per cent two days after admission. The working diagnosis was renal failure secondary to diffuse renal calcinosis and superimposed pyelonephritis.

Course in Hospital.—Cystoscopy was performed on the day of admission. No gross abnormalities of the bladder were encountered. A catheter was passed into the left ureter and a retrograde pyelogram on this side revealed only mild dilatation of the ureter. When the catheter was passed into the right ureter, obstruction was encountered in the terminal portion. This was by-passed by the catheter and milky urine was obtained. A catheter was left in the right ureter and a Foley catheter was placed in the bladder. On the third hospital day the catheters were removed because drainage was considered adequate and there was no evidence of obstruction. Penicillin and streptomycin were given to combat the urinary tract infection. The patient was continued on digitalis which had been started in the other hospital. On the fifth hospital day penicillin and streptomycin were stopped and Terramycin started. Polymyxin B was given from the sixth to the tenth hospital day because of the presence of *B. pyocyaneus* in the urine culture. Tarry stools were present on the second hospital day and vitamin K therapy was started. The patient's subsequent course was gradually downhill. Urinary output became less, vomiting of blood and tarry stools occurred despite vitamin K and whole blood transfusions. Despite restriction of fluid intake, edema fluid continued to accumulate. Two days before death his weight was 46 pounds (20.9 kilograms), 10¾ pounds (4.8 kilograms) greater than on admission. Uremic frost was first noted three days before death. Terminally the patient had a temperature of 102° F. The final event was ventricular fibrillation. Death occurred on the fifteenth day of hospitalization.

Laboratory studies were made daily. Results showed a constant anemia, normal white blood count until the last few days of life when it rose to 21,000 per cubic millimeter, platelet count which was never over 90,000. The CO_2 gradually returned to normal; chlorides were low, averaging 65 meq. per liter; sodium ranged about 120 meq. per liter; potassium was maintained about 6.0 meq. per liter; phosphorus remained elevated, 17 mg. per cent. The calcium gradually dropped, being 4.8 mg. per cent on day before death. The nonprotein nitrogen remained about 300 mg. per cent.

Autopsy was performed three hours after death. The body was that of a white male child measuring 105 centimeters and weighing 21 kilograms. There was pitting edema of the posterior scalp and scrotum in addition to a generalized nonpitting rubbery edema of the subcutaneous tissue of the entire body. A "Y"-shaped incision was made in the thorax and abdomen, revealing very edematous subcutaneous tissue and muscle. There was bilateral hydrothorax of approximately 40 c.c. each. No gross enlargement of the parathyroid glands was found. The lungs showed slight congestion and edema. The heart measured 9.5 cm. in greatest width and the thoracic cage at this level measured 17 cm. The heart weighed 116 grams (normal 86 grams). The heart was not remarkable grossly except for the hypertrophy of the musculature, the

Fig. 2.—Gross photograph of kidneys.

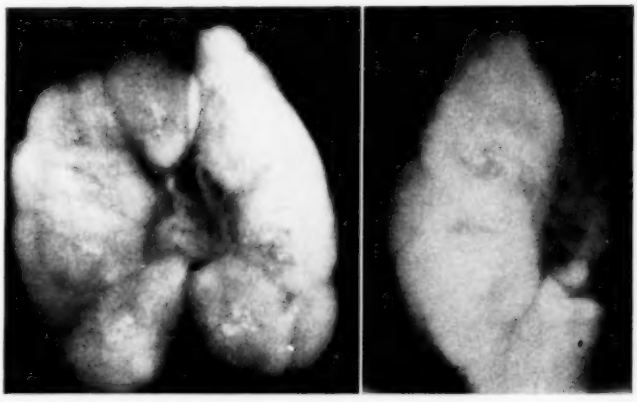

Fig. 3.—Roentgenogram of kidneys following removal at autopsy.

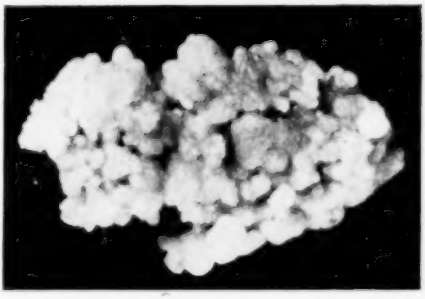

Fig. 4.—A 1 cm. calculus removed from upper calyx of right kidney at autopsy.

thickness of the left ventricular muscle being 14 mm. and the right 4 mm. There were approximately 150 ml. of clear fluid in the peritoneal cavity. The anterior liver edge was 3 cm. below the costal margin in the right midclavicular line and 7 cm. below the xiphoid process. The gastroenteric tract was normal except for small red elevations the size of a pinhead in the mucosa of the lower half of the colon. The mucosa between these lesions was edematous. The liver weighed 525 grams and grossly showed no abnormalities. The kidneys were equal in size and together weighed 97 grams (normal expected weight 129 grams) (Figs. 2 and 3). The capsules could be stripped with moderate ease and the underlying surface was slightly roughened and yellow. The ratio between cortex and medulla was about 1:2 and the demarcation was good. The cortex was yellowish white and somewhat paler than the medulla. One calculus measuring 1 cm. in diameter was found lying in the calyx of the upper pole of the right kidney (Fig. 4). The notable findings were the greatly increased resistance to cutting and the gritty feel of the cut surface of the kidney. The calyces and pelves were dilated and lined by thickened, wrinkled, white mucosa which showed focal areas of hemorrhage. The wall of the urinary bladder was thickened and the mucosa contained areas of hemorrhage. The ureteral orifices were dilated as were the ureters. The right testis was removed from the scrotal sac and grossly was not remarkable.

The Formalin-fixed brain weighed 1,205 grams and measured 17 by 12.5 by 12.5 cm. The cerebral vessels were engorged but no other gross abnormalities were noted.

Microscopic.—The lung sections showed mild interstitial edema. One section of the parathyroid gland was examined and was normal. The colon showed acute inflammation of the mucosa. The kidneys showed a diffuse deposition of a crystalline material throughout the parenchyma (Figs. 5 and 6). This material was doubly refractile and positive with the von Nossa stain (Figs. 8 and 9). In addition there was diffuse lymphocytic infiltration of interstitial tissue. The capsules of the glomeruli were often thickened and there were occasionally hyalinized glomeruli. The distal convoluted tubules in many instances contained purulent exudate. The ureters and urinary bladder showed a chronic inflammatory reaction and hemorrhage in the submucosa. Crystals similar to those in the kidneys were found in the section of testis (Fig. 7), in the thymus, in the spleen, and at the edge of the marrow cavity in the section of sternal bone marrow (Fig. 10). Of note in the latter section was the foreign body giant-cell reaction around the crystals.

Sections of the pituitary gland, aorta, thyroid gland, stomach, omentum, pancreas, diaphragm, liver, and adrenals were examined but exhibited no striking changes.

Brain: Seven large blocks from the brain and two blocks from the choroid plexus were examined histologically. The basal meninges showed mild fibrosis, a few round cells, and an occasional macrophage. A few macrophages containing hematogenous pigment and also occasional round cells were seen perivascularly in the brain substance. Swelling of oligodendroglia indicated cerebral edema and possibly renal failure. A search for clusters of oxalate crystals such as were seen in the various internal organs was fruitless. Under the polarizing microscope a few delicate double-refractile needles and minute prisms were found (1) in the brain substance, (2) between the villi of the choroid plexus, and (3) most often in the meninges, especially over the medulla oblongata. These crystals were scattered haphazardly in the interstices of tissues or more closely related to cells or other structures.

One section of the medulla oblongata was microincinerated at 450° C. and then treated with acetic acid; gas bubbles characteristic of oxalates did

Fig. 5.

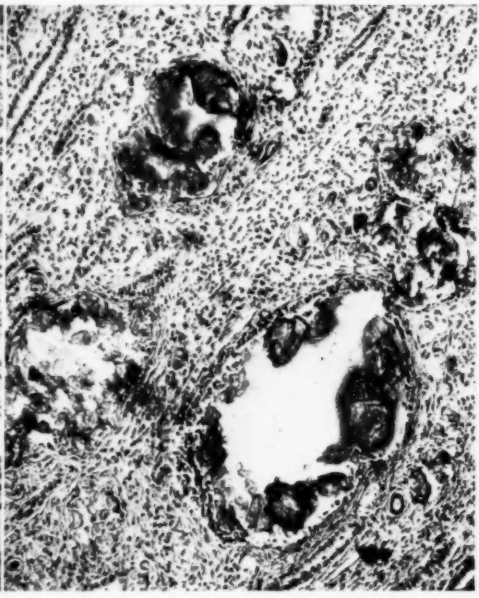

Fig. 6.

Fig. 5.—Photomicrograph of kidney showing calcium oxalate crystals, interstitial fibrosis and lymphocytic infiltrations. (H and E; ×140; reduced ¼.)

Fig. 6.—Photomicrograph of medullary area of kidney showing crystals, inflammation, and fibrosis. (H and E; ×140; reduced ¼.)

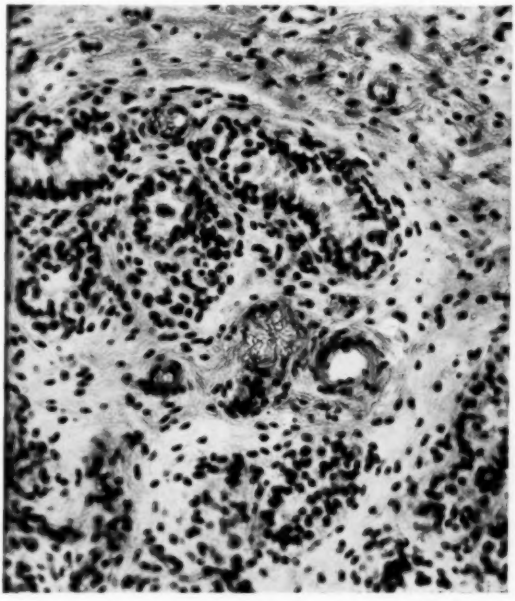

Fig. 7.—Photomicrograph of testis showing deposition of crystals. (H and E; ×280; reduced ¼.)

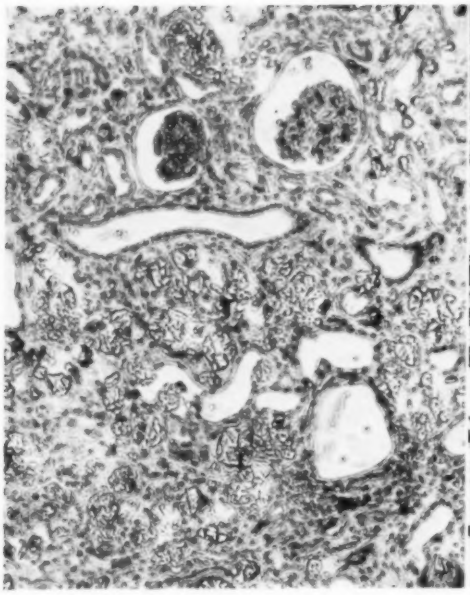

Fig. 8.

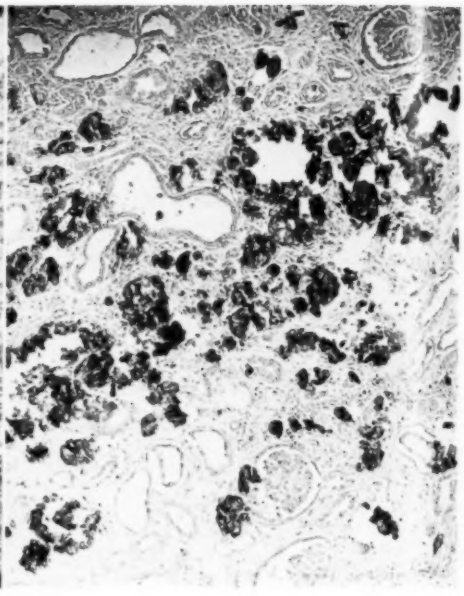

Fig. 9.

Fig. 8.—Photomicrograph of kidney showing crystals viewed with polarized light. (H and E; ×140; reduced ¼.)

Fig. 9.—Photomicrograph of kidney stained by von Kossa method. The crystals appear black. (von Kossa; ×140; reduced ¼.)

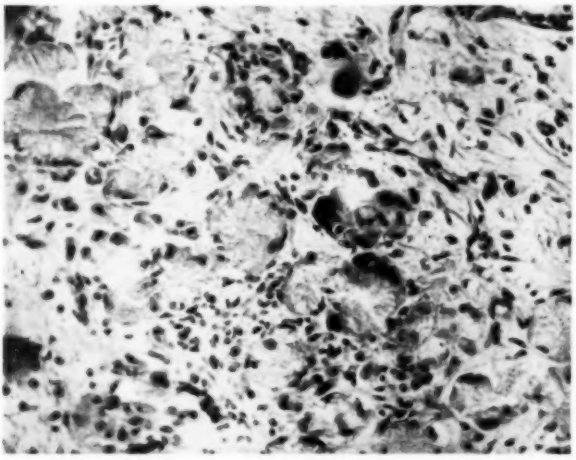

Fig. 10.—Photomicrograph of sternal bone marrow. Deposition of oxalate crystals is seen; foreign body giant-cell reaction is apparent about several of the crystalline masses. (H and E; ×400; reduced ¼.)

not appear. A von Kossa stain for demonstration of oxalates on a corresponding section was not convincingly positive.

The possibility that the histochemical methods employed are not sufficiently sensitive to identify minute oxalate crystals has been considered. Since no definite statement as to the nature and origin of the crystals seen in the meninges can be made, the evidence remains presumptive.

Chemical Analysis.—A renal stone was analyzed. The stone was ground to a fine powder, placed in a thin-walled parlodian tube of 0.5 mm. diameter and a Debye-Scherrer type x-ray photograph was taken using CuKa radiation and a camera of 57.3 mm. radius. The film showed the material to be 75 per cent crystalline. The only phase detected was calcium oxalate monohydrate, which showed that the specimen consisted largely of this material. Only crystalline materials are revealed in x-ray diffraction patterns. An analysis of a random piece of "Jores"-fixed kidney tissue revealed: calcium content per gram dry kidney, 144 mg.; oxalate precipitate per gram dry kidney, 276.6 mg. Only 52.4 per cent of the oxalate was in the form of calcium salt.

DISCUSSION

Jeghers and Murphy,[1] in their extensive review of oxalate metabolism in 1945, emphasized the enigmatic pathogenesis and the problematic treatment of oxalate calculi. Certain general facts pertinent to oxalate calculi are important. Thirty per cent of all calculi (in the United States) in the urinary tract are of oxalate origin. Calcium oxalate occurs in acid urine as do urates and thus combinations of these two are seen in calculi. Since calcium oxalate also occurs in alkaline urine, calculi in combination with amorphous phosphates can and do occur. However, the stone of the former type predominates. Heredity is usually not considered a factor with oxalate calculi, although Oram[2] studied a family in which calcium oxalate stones occurred in five generations. This inherited characteristic was dominant but occurred only in the males of the family. Jeghers and Murphy[1] have described four general types of oxalate stones: (1) the small, smooth, round or faceted stones, not larger than a pea, usually found in the renal pelvis or ureter; (2) the "mulberry" calculi of large size, most frequently found in the bladder; (3) the "jackstone shape," a rare type with projecting spurs, usually found in the bladder; (4) the "crystalline calculi" which are small stones with surfaces completely covered with sharp glistening crystals, an exceedingly irritating variety. Oxalate stones are opaque to x-ray and are probably the most radiopaque of urinary calculi.

Oxalate stones may occur with or without demonstrable calcium oxalate crystals in the urine, a factor which should be remembered in making a clinical diagnosis of oxalosis. Oxalate crystals in the urine were described on numerous occasions in the case reported here. Oxalate stones usually occur as noted above in the absence of infection. Hammarsten[3] produced calcium oxalate stones in rats experimentally, using a low magnesium, high oxalate, low vitamin diet with the urine sterile. She also succeeded in partially decalcifying these same kidney stones with diets rich in calcium, magnesium, and vitamins. Unfortunately these results have not been reproduced. Hammarsten suggests that the metabolism of oxalic acid is actu-

ally secondary and that calcium and magnesium metabolism are the important factors.

Jeghers and Murphy[1] gave the following as sources of oxalates: (1) food, actual and potential; (2) metabolic processes of certain intestinal bacteria and parasites; (3) intermediary metabolic activity of tissues. The third source remains in considerable controversy.

The actual metabolic fate of oxalic acid is still not certain. It can be stated that oxalates are excreted by the gastrointestinal tract and kidney, and may be excreted in the bile. Oxalates excreted are those ingested with food and also probably endogenous.

In our case the family history reveals four close relatives with severe renal disorders. Although stones were not found, the histories are certainly compatible with stones and the diagnosis of renal calculi seems most likely. Thus the history may or may not be significant with respect to an inherited defect. Three cases[4, 5, 6] similar to the present one have been reported in the literature. The ages of the patient were 4½ months,[4] 12 years,[6] and 7 years.[5] The clinical course in the prolonged cases was in many respects quite similar to this case, as were the gross and microscopic findings. The gross description of the kidneys in all cases is remarkably similar. Chemical analyses confirmed the composition of the crystals as predominantly calcium oxalate. The anatomic distribution of the crystals in these cases was interesting. In one,[5] crystals were widely distributed in body tissues, although most were in the kidneys and bone marrow. In the second case,[6] they were found in the kidneys and bone, vertebrae, rib, and sternum. In the third case,[4] crystals were found only in the kidneys. In the case reported here, crystals were found in thymus, spleen, kidneys, bone marrow of sternum, and the section of the testis. In other cases, where reported, the von Kossa stain reaction was variable. It was strongly positive in the case presented above. In Chou and Donohue's[5] case, no statement as to whether the crystals were von Kossa-positive or negative is made. In the case reported by Davis and associates[6] the von Kossa stain was negative, as was the alizarin red S stain for ionizable calcium. The latter stain was also negative in the present case. The role of infection in other cases and in the present one does not seem to be of significance in the etiology of the calculi.

The diagnosis of oxalosis should be suspected when diffuse intrarenal calcification, with progressive signs of uremia and failure of response to all therapy, occurs.

CONCLUSION

A case of oxalosis with diffuse intrarenal calcification and death due to renal failure is added to the literature. The question of inborn error of metabolism is again raised but no definite conclusions can be made.

ADDENDUM

Since this article was prepared for publication two additional case reports have been called to our attention. Burke and associates'[13] and Zollinger and Rosenmund's[14] cases are quite similar to our case.

We are indebted to the following: Miss Patricia M. Wirth of the Department of Research Medicine of the Children's Hospital of Pittsburgh for the analysis of we

kidney tissue; Dr. Leroy E. Alexander and Mr. Douglas T. Pitman of the Mellon Institute of Industrial Research for the x-ray examination of the renal calculus; and Mr. Albert Levin of the Department of Photography of the School of Medicine, University of Pittsburgh, for the photographs.

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RENAL GLYCOSURIA

Occurrence in Two Siblings and a Review of the Literature

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RENAL glycosuria, a congenital error in renal function, has been reported infrequently in the pediatric literature. Yet, its occurrence is frequent enough so that it must be considered in the differential diagnosis of melituria. The present report concerns two siblings admitted simultaneously to two different hospitals, in whom the diagnosis of renal glycosuria was made after routine urine analysis had revealed a reducing substance in the urine.

The first case reported is believed to be the youngest child discovered with this disease.

CASE REPORTS

Case 1.—M. L. (Bellevue Hospital No. 50127-53), a female infant, was born at Bellevue Hospital after an uncomplicated full-term pregnancy to a gravida v, para iv, 45-year-old white female; birth weight, 7 pounds. The mother had no glycosuria during this pregnancy, but was reported to have had it during previous pregnancies and was treated with insulin during one thirteen years previously.

The infant remained in the hospital because of social complications and at 4 days of age became febrile to 101° F. without apparent cause. Therapy was withheld and she reverted shortly to normal temperatures. At 3 weeks of age, a severe diaper rash was first noted. At that time, she weighed 8 pounds. At 4 weeks of age, she had several loose, foul stools; examination revealed a mild impetigo, left otitis media, pharyngitis, and an 8-ounce weight loss. Treatment was instituted with procaine penicillin. At this time (one month of age), urine examination revealed the reaction to be acid, reducing substance 3 plus, acetone trace, and many clumped white blood cells. This was a noncatheterized specimen. Urine culture on a catheterized specimen grew out *Bacillus proteus* and the infant was treated with Gantrisin.

Further investigation was instituted to determine the cause of melituria. Fasting blood sugar was 96 mg. per cent. All blood sugars in this case were done on capillary blood which is up to 20 mg. per cent higher than simultaneous venous blood and is believed to be a more accurate method for determining blood sugars.[1-5] A catheterized specimen of urine was obtained and the reducing substance identified as glucose by the osazone and Selivanoff tests. Subsequent urines, both in the fasting and postabsorptive states, were found to be strongly positive for glucose and, after the first two specimens, free of acetone. White blood cells and casts cleared rapidly on therapy.

Subsequent investigation consisted of oral and intravenous glucose tolerance curves, insulin tolerance test, and repeated fasting blood sugars with simultaneous urines. These latter urines were constantly 3 to 4 plus positive for glucose. Two fasting blood sugars were above 110 mg. per cent but the glucose tolerance curve on those occasions was normal as were all other tests. A twenty-four-hour urine

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specimen was not found to have any abnormal content of amino acids. Blood counts were normal. Blood chemistries revealed the following: CO_2, 20.7 meq. per liter; nonprotein nitrogen, 35 mg. per cent; calcium, 9.4 mg. per cent; phosphorus, 5.2 mg. per cent; chloride, 104 meq. per liter; cholesterol, 164 mg. per cent; cholesterol esters, 92 mg. per cent; bilirubin, 0.45 mg. per cent; and, thymol turbidity, 5.2 units. Mantoux in 1:100 dilution was negative.

On the basis of constant glycosuria, lack of organic renal pathology, lack of evidence for diabetes mellitus, and identification of glucose in the urine, a diagnosis of renal glycosuria was made. The infant had been gaining weight slowly and extra glucose was added to the diet as a precautionary measure which, however, did not change the weight course. The most vexing problem was an almost constant diaper rash that required unusual attention on the part of the nursing staff for its control. She remained afebrile throughout her course.

Case 2.—J. L. (Lenox Hill No. 10226/17224), a 16-month-old white male, was admitted to Lenox Hill Hospital for surgical correction of strabismus. His past history revealed that he was born after a full-term pregnancy that was complicated by glycosuria. Delivery was normal and birth weight was 10 pounds. At 11 months of age, he was admitted to a foundling hospital because of social conditions.

After admission to that hospital, he developed conjunctivitis and upper respiratory infection, then a cervical abscess, and again conjunctivitis and an upper respiratory infection, each of which, in turn, responded to antibiotic therapy. Laboratory work revealed a normal blood count and a urine containing a few white cells and a reducing substance. All urine analyses were positive for reducing substance from 2.0 to 2.8 per cent. The fasting blood sugar on three occasions was 96, 85, and 86 mg. per cent. An oral glucose tolerance curve was normal.

On admission to Lenox Hill Hospital, the patient weighed 24 pounds and was found to have strabismus and pharyngitis. The latter responded well to Aureomycin. Further examination revealed that the urine contained over 2 per cent reducing substance which was identified as glucose and was present whether or not the urine was obtained in the fasting state. Laboratory data: CO_2, 32.4 vol. per cent in the fasting state and 62.6 vol. per cent postprandial; the postprandial phosphorus level was 4.7 mg. per cent. Other chemistries showed the following: blood urea nitrogen, 15.9 mg. per cent; creatinine, 0.6 mg. per cent; cholesterol, 187 mg. per cent; and, cholesterol esters, 127 mg. per cent. Oral glucose tolerance curve was normal. Skull roentgenograms, intravenous pyelogram, and electroencephalogram were normal. The diagnosis was renal glycosuria.

Investigation of the family of these two children revealed that the mother, a 46-year-old white female, had a 1 plus reducing substance in her urine in the fasting state with a blood sugar of 106 mg. per cent and a normal oral glucose tolerance curve. She had no family history of diabetes. She probably has renal glycosuria. The father, white, 53 years of age, had no personal or family history of diabetes. Repeated casual urines and others taken simultaneously with fasting blood sugars were free of reducing substance. His oral glucose tolerance curve was normal. He is apparently free of the disease.

The two siblings reported were the offspring of the above-mentioned parents. Three other children of the mother, each of different paternity, had urines collected in the fasting state. These were free of reducing substances.

REVIEW OF THE LITERATURE

Klemperer,[6] in 1896, first called attention to the occurrence of glycosuria without hyperglycemia. Since then, the disease has been well recognized

and there have been numerous case reports.[1, 7-10] Few, however, have appeared in the pediatric literature.[8, 11]

The incidence reported varies widely, possibly because of different diagnostic standards. Bland[1] reported a rather low incidence for the general population of 0.09 per cent, while other estimates vary from 0.17 to 2.0 per cent.[12-15] The latter figure was based on a study of 70,000 selectees in the United States during World War II.[15] Ralli[16] found renal glycosuria in 7 of 400 cases of diabetes mellitus under study, and Blotner and Hyde[14] reported 8.9 per cent of 367 cases of melituria. Lawrence,[2] whose diagnostic standards differ from those generally used, found renal glycosuria in 65 per cent of all cases of glycosuria examined in England during World War II. White[13] studied 3,144 cases of melituria in children with an incidence of renal glycosuria of 0.3 per cent. The familial incidence has long been observed. Hjarne,[17] in his classical study, found that in seven generations of one family, constituting 149 individuals, seven of them had diabetes mellitus and eighteen had renal glycosuria. In Marble's series,[18] 75 per cent had a family history of the disease, and in White's series,[13] 100 per cent. Brown and Poleschuck[7] reported four cases in three generations of one family. It is believed that the disease is probably inherited as a Mendelian dominant.

The diagnosis of renal glycosuria can only be made after certain criteria have been met. The condition is considered to be asymptomatic although polydipsia and polyuria may be complaints. The disease is usually discovered in the investigation of an accidentally discovered asymptomatic glycosuria. To begin with, the use of the Benedict reaction for the detection of glucose must be carefully interpreted, since reducing substances other than glucose, such as other saccharides, creatinine, uric acid, homogentisic acid, ascorbic acid, formaldehyde, etc., can give a positive reaction. When melituria (the presence of a sugar in the urine) has been established, the type of carbohydrate must be identified, since other monosaccharides and disaccharides are found in the urine in other disorders. Lactose, galactose, maltose, mannoheptose, pentose, fructose, and sucrose are mentioned by Marble[18] as being among the less common meliturias. Glucose can be identified by the osazone and Selivanoff reactions.

Glycosuria (the presence of glucose in the urine) may be classified as hyperglycemic (diabetes mellitus, hyperthyroidism, hyperpituitarism, hyperadrenalism, hepatic insufficiency, asphyxia, etc.) or normoglycemic (nephrosis, nephrosclerosis, pyelonephritis, renal glycosuria, phlorhizin poisoning, and heavy metal poisoning). Marble[18] established the generally accepted criteria for renal glycosuria in 1932, as follows: (1) glycosuria without hyperglycemia, independent of diet and present in all specimens; (2) fasting blood sugar less than 120 mg. per cent and postprandial less than 170 mg. per cent; (3) normal glucose tolerance curve with no values over 170 mg. per cent and return to control levels in two hours; (4) proof that the sugar is glucose; (5) no symptoms of diabetes mellitus; (6) no progress toward diabetes mellitus; (7) family history of glycosuria should be present; (8) carbohydrate metabolism should be normal as evidenced by a

normal respiratory quotient and a drop of serum inorganic phosphorus after glucose ingestion. Lawrence,[2] however, does not feel that glycosuria must be present in the fasting state. Conditions causing temporary glycosuria, such as severe infections, mumps, head injuries, and poisonings, should be considered in the differential diagnosis.

The pathogenesis of renal glycosuria has been the subject of extensive investigation. It has been well established[5] that blood glucose passes freely from the plasma into the glomerular filtrate, reaching equilibrium at the glomerular level. Under normal conditions, it is completely reabsorbed from the glomerular filtrate at the proximal tubular level of the nephron, so that none appears in the urine. It is believed that an enzyme system—phosphorylase—is essential for this reabsorption. The maximal ability for the tubule to reabsorb glucose has been expressed as Tm_G. This level can be reached and surpassed by raising the plasma level of glucose, so that more will be filtered than can be reabsorbed. At this point, glucose will appear in the urine. This "threshold level" above which glucose will appear in the urine is commonly accepted as 160 to 180 mg. of glucose per 100 ml. of plasma.[5] With relation to this level, individuals with glycosuria may be divided into those with a normal threshold and hyperglycemia and those with a depressed threshold and normoglycemia.

Bland[1] postulated three possible mechanisms for renal glycosuria, as follows: (1) decreased phosphorylase in proximal renal tubule; (2) hormonal control of renal threshold; (3) impaired renal function due to degeneration secondary to repeated infection. Phlorhizin, a nephrotoxic drug, regularly induces renal glycosuria. Its mechanism of action is believed to be the inhibition of phosphorylase.[5] Lead, mercury, and possibly uranium poisoning may cause renal glycosuria by the same mechanism. Farber and associates[19] reported a variation in the Tm_G with the administration of insulin in diabetes mellitus, demonstrating possible hormonal control of glucose reabsorption. Renal glycosuria of pregnancy is another possible hormonal effect. Callaway[20] reported a case of renal glycosuria complicating diabetes mellitus. The constant glycosuria was ameliorated when one kidney, which was the site of chronic pyelonephritis, was removed. Renal blood flow and glomerular filtration rate have been shown to be normal in the disease.[21] Ralli[16] reported normal PSP excretion and urea clearance in her case.

The data that have been accumulated indicate that the most likely mechanism is a depression of the renal threshold for glucose due to a lack or inhibition of the phosphorylating mechanism in the proximal renal tubule. However, Friedman and coworkers,[21] in testing seven controls and five renal glycosuries, found that the apparent inability of the glycosuries to reabsorb glucose at low plasma levels (100 mg. per cent) disappeared at much higher levels (200 to 400 mg. per cent). They postulated that there may not be a true entity of renal glycosuria but rather an iatrogenic disease caused by our too close adherence to a supposed normal level of tubular reabsorption. Reubi[22] reported a similar observation in a recent study of nine cases. He reports two differ-

ent types of renal glycosuria. The first, called "true renal diabetes," is marked by glycosuria with a low Tm_G. This is congenital and familial, and due to an impotency of the proximal tubule. The second type (similar to Friedman's cases) demonstrates a low Tm_G at low blood glucose levels and a normal Tm_G at high levels. This "renal pseudodiabetes" he believes to be inherited or acquired and to be due to an increased dispersion in the glomerular tubular activity. Myerson and Pastor,[23] in a somewhat encompassing view, regard renal glycosuria as one of a group of "unifactoral" tubular resorptive deficiencies among which they number nephrogenic diabetes insipidus, vitamin D resistant rickets, hyperchloremic renal acidosis, etc., as opposed to "multifactoral" deficiencies among which they discuss the Fanconi syndrome, cystinosis, glycosuric rickets, etc.

The prognosis for renal glycosuria is favorable. It is considered a benign disease. Lawrence[2] and Hjarne[17] state that there is no transmutation or degeneration of renal glycosuria to diabetes mellitus. These two diseases are believed to be transmitted by two separate autosomal genes.[24, 25] The former is probably a Mendelian dominant. However, the incidence of diabetes mellitus is known to be higher in families in whom renal glycosuria exists than in the general population.[17] Thus, some genetic linkage between these two diseases is a possibility. It is also conceivable that an individual with renal glycosuria possessing certain favorable conditions, such as obesity or arteriosclerosis, could develop diabetes mellitus as an unrelated disease. Renal glycosuria appears to be permanent; however, partial or complete disappearance has been reported due to nephrosclerosis or nephritis occurring in a patient with renal glycosuria.

There is no specific treatment for this disease. Some workers have advised the addition of glucose to the diet to replace that lost in the urine. It would seem that with a lowered Tm_G, additional glucose would only serve to cause diuresis. It might be wise to supply additional calories in the form of fat. Diaper dermatitis in infants due to the glycosuria demands constant attention.

SUMMARY

Renal glycosuria occurring in two siblings is presented. The younger was one month old at the time of diagnosis.

The literature is reviewed with the following conclusions:

1. The most likely mechanism is an absence of, or impaired function of, phosphorylating enzymes in the proximal tubule vital for the resorption of glucose. As a result, the threshold is lowered.

2. Renal glycosuria is benign and does not transmute or degenerate into diabetes mellitus.

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Was It Wilms' Tumor?

Tuesday a Child of Mr. ---------- Turner, a Carpenter at the North-End, about 4 Years of Age, died after a lingering Indisposition, which was suppos'd to have been a Dropsy; but after the Child's Death, the Body was opened, and there was found a Piece of Flesh growing to the Kidney, which weighed above Nine Pound Weight.

MASS. GAZETTE AND BOSTON NEWS LETTER, OCTOBER 20, 1763.

TOXOPLASMOSIS IN INFANTS

Report of Two Cases

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TOXOPLASMOSIS in infants and children was infrequently recognized in the past. Recent studies by Sabin and his co-workers[1] suggest that the incidence may be considerably higher than was previously suspected.

Toxoplasma is a protozoan parasite first described by Nicolle and Manceaux[2] in 1908 in the gondi, a North African rodent, and at almost the same time by Splendore[2a] from Brazil in the rabbit. Since then toxoplasma has been reported in a large number of species of mammals, reptiles, and birds from many parts of the world. The first case of human toxoplasmosis was reported by Janku,[2b] though the organism was not identified until subsequent studies by Wolf and Cowen.[3] This, however, is generally accepted as the first case of human toxoplasmic infection. Torres,[4] in 1927, reported the second case of human infection. Wolf and Cowen[3] described the third case occurring in an infant with complete clinical and pathologic studies in 1937.

An extensive study and review of the literature up to 1943 is presented by Callahan and associates.[5] It has been shown that toxoplasma may be transmitted transplacentally from a mother who herself does not have clinical evidence of the disease but who has had serologic evidence of it. This is the so-called "congenital toxoplasmosis." It has been suggested that the infection may be transmitted by direct contact with the infected tissues as well as excreta, or by such vectors as ticks and flies. Attempts to transmit the disease by fleas, lice, and mites have not been successful.

Following is a history and findings in a case which we believe is one of congenital toxoplasmosis.

Case Reports

Case 1.—K. M., a white female, aged 3 weeks, was admitted to Sarah Morris Hospital. Birth history and prenatal records were normal. No abnormalities were noted in the first week of life. By the second week of life, the infant became exceedingly lethargic and began to regurgitate feedings. Physical examination revealed a lethargic infant with a weak cry. The liver and spleen were found to be enlarged. The anterior fontanel was somewhat depressed and the mucous membranes were dry. The skin turgor was poor. Intravenous fluids and plasma were administered and the infant responded rapidly to therapy. The eye grounds were examined by an ophthalmologist and found to be normal. A spinal tap was done because of the marked lethargy. Viscid xanthochromic spinal fluid was obtained which coagulated on standing. The cell count was 660 total cells (red blood cells, 600; white blood cells 60 per cubic millimeter); sugar 25 mg. per cent; protein 1,100 mg. per cent. The temperature ranged widely from 99° to 107° F. during the first week of hospitalization. Tremors of the hands and feet developed on the fifth hospital day; a subdural tap

From the Sarah Morris Hospital for Children of the Michael Reese Hospital.

was done and 2 c.c. of xanthochromic fluid was obtained. The blood count revealed an eosinophilia of 15 per cent at this time. Hemoglobin was 70 per cent; red blood count 3.2 million per cubic millimeter, white blood count 10,000 per cubic millimeter; sedimentation rate 20; urine examination was normal.

Progress.—Regurgitation of feedings persisted for ten days and stopped spontaneously, but the inability to maintain stable body temperature persisted along with lethargy. The anterior fontanel continued to feel tense and bulged. Two weeks after admission, a toxoplasmin skin test was found to be negative. It was discovered that

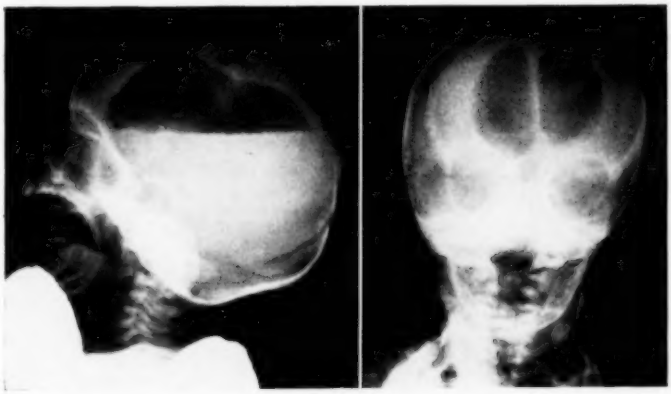

Fig. 1.—Pneumoencephalogram demonstrating hydrocephalus and enlarged ventricles.

Fig. 2.—Encircled region of brain at autopsy, revealing multiple areas of gross calcification.

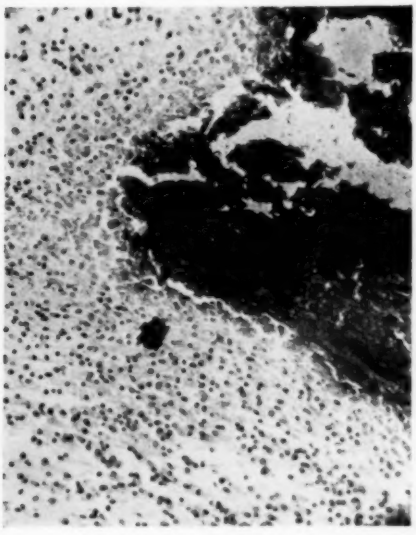

Fig. 3.—Microscopic section through cortical region of brain, demonstrating calcification.

the father had a strongly positive skin test and the mother had a negative skin test for toxoplasmosis.

Skull x-rays of the infant revealed intracranial calcifications in the left frontoparietal region. Ventriculography revealed marked generalized dilatation of the entire ventricular system through the third ventricle (Fig. 1). Further demonstration of scattered calcifications in the region of the caudate nucleus and brain substance of the left temporal and parietal region were clearly noted (Fig. 2).

The child's clinical course appeared to improve for several days during which time she began to retain food and gained weight. Circumference measurements of the head, however, demonstrated a gradual increase in size. The infant became markedly lethargic and extremely pale.

A Sabin dye test[6] was performed by the United States Public Health Service Laboratories in Chambles, Georgia, on the blood obtained from both mother and infant. The results revealed the titers in the mother to be 1:4016 and in the infant 1:16384. The upper limits of normal are in the range of 1:256.

The child died 62 days later, at the age of 3 months, following a sudden convulsion.

Post-mortem findings at the Sarah Morris Hospital were confined chiefly to the central nervous system. Examination of the brain revealed marked internal and moderate external hydrocephalus. Microscopic study demonstrated a granulomatous encephalitis with multiple calcifications (Fig. 3). The reticuloendothelial system was also involved with the findings of hyperplasia of mesenteric lymph nodes and granulomatous lesions in an enlarged spleen. Microscopic sections through the liver revealed multiple areas of focal necrosis with collections of polymorphonuclear cells. Moderate fibrosis of the thymus and thyroid were also observed. Examination of the lungs revealed a moderate pulmonary edema.

CASE 2.*—A 21-month-old white female was examined at the Sarah Morris Hospital for children in 1935, following a convulsion. The child was observed to be in a posteonvulsive stupor. A spinal tap revealed 23 white blood cells with a positive Pandy. The infant remained in the hospital for only a few days and was discharged following a negative physical examination. The diagnosis of idiopathic convulsions was suggested.

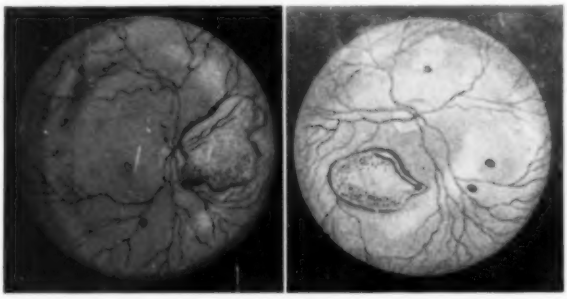

Fig. 4.—Photograph of painting, demonstrating chorioretinitis seen in toxoplasmosis.

Two years passed and another episode of convulsions occurred unrelated to any illness or fever. No cause could be elicited for this episode.

In 1941, six years later, the diagnosis of idiopathic epilepsy was made following the third seizure. It was not

*Prepared from progress notes of a clinical case of toxoplasmosis through the courtesy of Dr. Ralph H. Kunstadter, attending physician, Sarah Morris Hospital for Children, Chicago, Illinois.

until 1943 that skull x-rays revealed calcifications scattered throughout the cerebral cortex. Vision in the left eye was also noted to be poor and funduscopic examination revealed a chorioretinitis (Fig. 4).* The right leg was noted to be weaker and thinner than the left leg, with apparent signs of atrophy. Shortly thereafter, right-sided pyramidal signs developed. The child remained well, apparently with no increase in symptomatology for the next four years, except for an occasional headache and scotoma. There was no progression of the chorioretinitis. Phenobarbital was given prophylactically.

At the age of 10 years (1949) she had her first menstrual period which was considered normal.

The first records of positive skin tests for toxoplasmosis in both the child and her mother were recorded at the age of 10 years. An older sibling demonstrated a negative skin test. Complement fixation tests for toxoplasmosis were negative in the mother and older sibling, but strongly positive in the child with the disease.

This child has been followed to her twenty-second year of life in the clinic with only an infrequent episode of petit mal type convulsions and an occasional headache.

DISCUSSION

The pathology of toxoplasmosis in infants generally consists of granulomatous type lesions and areas of necrosis in the brain and spinal cord. These areas frequently become calcified and harbor the parasite. In adults an infection with toxoplasma frequently becomes generalized, whereas in infants and children it is recognized chiefly in the central nervous system.

In early life, clinical symptoms may be predominately neurological, such as convulsive seizures, retraction of the head and stiff neck. Shortly after birth an internal hydrocephalus of the obstructive type may develop. Spasticity, opisthotonos, or paralysis may also be demonstrated on physical examination. Ocular pathology in the form of chorioretinitis with focal areas of involvement has been described. Less specific complaints such as feeding problems, vomiting, diarrhea, and upper respiratory infections may be presented. Hemorrhagic tendencies with anemia, splenomegaly, hepatomegaly, jaundice, and purpura have also been described in congenital toxoplasmosis. No specific urinary findings can be correlated with this disease. The cerebrospinal fluid, however, more frequently exhibits an increased amount of protein and may be xanthrochromic. Roentgenograms of the skull may demonstrate multiple foci of intracerebral calcifications.

The diagnosis of the disease is further aided by the use of demonstrable neutralizing antibodies in the skin of rabbits. A more practical test described by Sabin[7] is the dye test, and it demonstrates titer increases in the blood of infected hosts.

The diagnosis of congenital toxoplasmosis cannot be made in the absence of dye test antibody in the child, regardless of how high the titer may be in the mother's serum.[8] A positive diagnosis can be made when the dye test is 1:256 or more in both the mother and child, provided the child is over 4 months of age. When a high titer is obtained in an infant during the first weeks of life, the test should be repeated at the end of four months. If the high titer was due to infection

*Photograph of funduscopic changes in the chorioretinitis of toxoplasmosis through the courtesy of Dr. B. M. Kagan, chairman, department of pediatric research, Michael Hospital, Chicago.

with toxoplasma, it will still be high in the second test. If the second test is negative, or the titer has fallen, the diagnosis of toxoplasmosis cannot be made, because the result of the first may have been due to passive transfer of antibody from the mother.

When a high dye test titer is obtained in an infant during the first weeks of life, a complement fixation test should also be done on both the mother and child. If the mother has high titers in both tests, and the child has no complement fixing antibodies, the results are indicative of a current, active infection with toxoplasma, which should be treated. Nevertheless, as stated above, the tests should be repeated a few months later to determine if the previously determined antibodies were passively transferred.

In older children, particularly over the age of 6 years, when the dye test titers may be less than 1:256 in the mother or child, or in both, the diagnosis can still be regarded as highly probable if the child exhibits clinical manifestations that are compatible with congenital toxoplasmosis.

When only the mother's serum is available for examination in cases where the child died before congenital toxoplasmosis was suspected, a dye test titer of 1:96 or more in the mother does not prove that the infant was infected with toxoplasma, but a negative test, or a low titer within three years after delivery, indicates that the child did not have toxoplasmosis.

No successful therapy is yet available against this organism. The most promising recent drug against toxoplasmosis is a pyrimidine substance called Daraprim which has shown some benefit in experimental infections and acts synergistically with the sulfonamides.[9]

SUMMARY

The foregoing presentation was that of a case of congenital toxoplasmosis in a 3-week-old white female. Clinical and pathologic changes during life and at post mortem have been discussed. Diagnostic procedures performed, viz., the Sabin dye test, x-ray of the skull for intracerebral calcification, and pneumoencephalography were of value in arriving at a diagnosis. A case of convulsions observed in a clinic which ultimately was diagnosed as toxoplasmosis and was followed through the twenty-second year of life is also included. A brief review of the literature on toxoplasmosis has also been noted.

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CARDIAC ARREST DURING EXCHANGE TRANSFUSION

Successfully Handled with Thoracotomy and Cardiac Massage

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EXCHANGE transfusion is a well-accepted procedure in the treatment of erythroblastosis fetalis. Although profound changes in homeostasis might be expected, most babies withstand the procedure uneventfully. Many factors are present during the course of an exchange transfusion which might predispose to cardiac arrest. This report will include a discussion of some of these factors.

CASE REPORT

This infant was born on Dec. 29, 1954. Because of a strong family history, the family physician, Dr. Harold P. O'Neill of Albany, Oregon, was immediately alerted to the possibilities of erythroblastosis fetalis. The two older siblings had been normal, the third child was jaundiced and required five transfusions. The fourth and fifth children died at three days and seven hours, respectively, the cause of death being erythroblastosis fetalis. The original Rh determination on this baby was reported to be negative; however, the next day he was found to test positive. He was transferred to Sacred Heart General Hospital because of this finding, a profound bleeding tendency, and a positive Combs test.

Physical examination on admission revealed mild edema, no marked icterus or hepatosplenomegaly. A puncture wound site on the left heel was bleeding freely and did not stop with pressure. The baby was active. Examination of the chest was within normal limits. No murmur was heard. The hemoglobin was 12.9 grams, the red count 4.52 million, the white count 20,600, with 62 per cent polymorphonuclearcytes, 3 per cent eosinophils, 29 per cent lymphocytes, and 4 per cent monocytes. There were 2 per cent neutrophilic metamyelocytes and 8 nucleated red cells per 100 white cells. A rather remarkable finding was a prothrombin time of 258 seconds. The bleeding time was 3 minutes, coagulation time 9½ minutes. The platelet count was 150,000 per cubic millimeter. Clot retraction was complete in six hours.

An exchange transfusion was believed indicated in this patient, primarily because of the severely prolonged prothrombin time and bleeding tendency, and also because of the profound family history. The procedure was carried out in the usual manner, through the umbilical vein, using citrated blood less than twenty-four hours old. After about 350 c.c. had been introduced, a new bottle was added. Shortly thereafter, the apical pulse beat was noted to be absent. An endotracheal tube was introduced and adequate oxygenation was maintained with the anesthesia machine, and within about 90 seconds an oblique intercostal incision of the fourth interspace was made without preparation. One and then two fingers were introduced and the heart, which was apparently arrested in systole, was gently massaged. The incision was carried downward in the parasternal

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area, cutting three costal cartilages. With more effective massage a normal cardiac rhythm returned in about two minutes. Since at the time of cardiac arrest we were somewhat behind in the exchange transfusion, and because of the blood loss from the thoracotomy, we elected to resume the exchange transfusion in the usual manner. This was done while the chest was open and it was noted that when blood was introduced the heart was definitely cool. Marked slowing of the heart resulted and massage was reinstituted. Two cubic centimeters of 1:10,000 Adrenalin was injected into the left ventricle because of the rather weak pulsation. Following this, spontaneous respirations were initiated and the cardiac rhythm returned to normal. The exchange transfusion was then completed uneventfully. A chest tube was placed in the dependent portion of the chest. The cartilages were reapproximated with No. 32 wire and the wound was closed with two layers of continuous 00 plain catgut and continuous cotton to the skin. The exchange transfusion was completed, with 560 c.c. of blood introduced and 500 c.c. removed.

A number of chemical determinations were made on the blood removed shortly after the cardiac arrest in an attempt to explain why it might have occurred. Sodium was 113 meq. per liter; potassium 4.5 meq. per liter; chlorides 99.7 meq. per liter; CO_2 7.7 mm. per liter; calcium 2.85 meq. per liter; inorganic phosphates 11.5 mg. per cent; sugar 156 mg. per cent; blood urea nitrogen 48 mg. per cent.

The infant was returned to the ward and kept in an Isolette with oxygen and full humidity. Special nursing was provided. He was treated with parenteral penicillin, Aehromycin, and streptomycin, as well as vitamin K. Convalescence was complicated by an episode of twitching and unpredictable respiration, which was interpreted as tetany. This was corroborated by the finding of the low serum calcium. The patient responded to 4 c.c. of calcium gluconate intravenously and was kept on a formula of Bremil and given 1 Gm. of calcium lactate with each feeding. He later had a short seizure, characterized by slow rhythmical clenching of the fists and cyanosis, and responded nicely to intravenous calcium gluconate again. By the fifth postoperative day the left upper lobe appeared partially atelectatic on x-ray. The chest tube and sutures were removed. A mild wound infection required some attention. Thoracentesis resulted in the aspiration of 20 c.c. of air. The serum bilirubin remained consistently low but the hemoglobin gradually dropped to 8.8 grams. Shortly before discharge the patient received two 50 c.c. transfusions by scalp vein. At all times the neurological examination was within normal limits. The baby continued to have a good Moro reflex; he ate well and was not listless. The wound healed completely, and the baby was discharged from the hospital at 2 weeks of age. He has been followed closely as an outpatient and his progress has been very satisfactory. The lung has expanded completely and the heart is apparently normal. The baby has a good appetite and is gaining well.

DISCUSSION

It is interesting to speculate on the possible causes of this baby's cardiac arrest during exchange transfusion. The low serum calcium immediately after the cardiac arrest is the best objective evidence that we have. Increased potassium in the donor blood from destroyed cells is not a likely factor since this blood was less than twenty-four hours old. It is conceivable that the blood citrate in the baby was raised to toxic levels since animals subjected to similar procedures develop cardiac fibrillation and arrest, particularly of the right ventricle.[1] The temperature of the donor blood is a potential factor. The first bottle had been adequately warmed, but apparently the second bottle to be used

was not as well warmed; in fact, the heart was noticeably cooled when this blood was injected and the rate and force of cardiac pulsations were diminished concurrent with this cooling. Marting and associates[2] have recently advocated the use of warm blood for exchange transfusions. Two types of blood warmers are described. Monitoring babies with electrocardiograms during injection of cold and warm blood is suggested. This is a preliminary report which deserves consideration. The cardiac arrest was not related in time to the introduction of 10 per cent calcium gluconate intravenously as has been our custom after the introduction of each 100 c.c. of blood. Some of these difficulties might be alleviated by using only fresh, warm blood, preferably heparinized, to eliminate the citrate factor. Such a practice necessitates an adequate donor list available on call as the need arises. The blood may then be drawn into an heparinized bottle a short time before the exchange transfusion is to be carried out. This blood, of course, is not cooled. That the presence of a trained observer, watching the baby's pulse, respirations, and appearance during the procedure is advisable, is well brought out in this case.

SUMMARY

1. A case of cardiac arrest occurring during exchange transfusion for erythroblastosis fetalis is recorded.

2. The arrest was successfully handled by thoracotomy and cardiac massage.

3. A discussion of some of the potential precipitating factors is presented.

4. Suggestions for eliminating some of these factors are presented.

I should like to express my gratitude to Drs. Charles W. Fluke and Robert L. Bowen, who were immediately available and to whom the major credit for success of the procedure is due.

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THE TREATMENT OF ECZEMA IN INFANTS AND CHILDREN

PART IV

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"Immunology is a mixture of established fact, half knowledge, hopeful guessings and frank bewilderment."

—*W. W. C. Tapley: An Outline of Immunity*, William Wood & Co., 1933.

ATOPIC DERMATITIS

ATOPIC dermatitis is brought about by the same abnormal constitution which underlies hay fever and asthma, and is often the first manifestation of this constitution. It is not uncommon for children to be afflicted with all three at the same time. About half of the infants who have atopic dermatitis later develop respiratory allergy. Atopic dermatitis is a disease of the young, although it may last well into adult life, and is occasionally even seen in the aged. Although it has been called by different names at different age periods, it is one and the same disease at all ages, and is best called atopic dermatitis at all ages.[11] It is as much a constitutional disease as diabetes or pernicious anemia; what retards the treatment more than anything else is that it is not possible to change the constitution that is responsible for it. Like asthma, its fundamental basis is abnormal immunology, and, also like asthma, other stimuli not related to immunology, particularly psychologic, may greatly aggravate it.

IMMUNOLOGIC TREATMENT

In order to make an attempt to understand the rationale of immunologic treatment it is first necessary to consider in some detail the immunophysiologic principles involved. The antibody (atopic reagin) which has to do with atopic dermatitis is fixed in the vascular loops in the papillae of the corium, and can often also be detected in the blood, contained mostly or possibly entirely in the gamma globulin fraction. The commonly accepted theory has been that when antigen, inhaled or ingested, reaches the sensitized skin tissue, an immunologic reaction results with the production of an irritating end product, possibly histamine, and consequent dilatation and increased permeability of the small cutaneous vessels, with a resulting inflammatory reaction and the histologic changes of eczema.

There are those who have said that scratch or intracutaneous tests are entirely useless in the determination of etiology, and that the immediate urticarial type reaction so obtained has nothing to do with the eczema, for the eczematous reaction is a delayed twenty-four-hour type reaction, and is vesicular or papular and never urticarial. In order to determine etiology the test reaction should produce the

Editor's Note: Despite the notice in the August issue that reprints would not be available of Dr. Hill's series of papers on "The Treatment of Eczema in Infants and Children," many requests are being received. As previously stated, no reprints are available as the articles will be published in book form.

[11]Hill, L. W., and Sulzberger, M. B.: Evolution of Atopic Dermatitis, Arch. Dermat. & Syph. 32: 451, 1935.

lesion of the disease in the same way that eczema (the lesion of the disease) is produced by the patch test. There is some evidence in favor of this point of view, and some against it.

1. The skin of a patient who has ragweed hay fever gives an immediate urticarial type scratch or intracutaneous test. So does the skin of a patient who has atopic dermatitis due to ragweed pollen, and only very rarely a positive patch test. If the urticarial type skin test is of etiological significance in atopic dermatitis due to ragweed, why do not all patients with ragweed hay fever who show this test have atopic dermatitis as well?

2. If a person with hay fever but no eczema is given too much ragweed extract by inoculation, he is likely to develop urticaria, practically never eczema. A person with atopic dermatitis from ragweed, with or without hay fever, has exactly the same sort of skin test that the person with hay fever alone has. Yet his tolerance to injected ragweed extract is very low, much lower than that of the patient with hay fever alone, and if he is given any but a very small dose of ragweed extract his existing eczema will probably become worse, and he is likely to develop new eczema in places where he did not have it before. This is a delayed twenty-four-hour type reaction. The amount of antigen when injected or ingested which will worsen eczema or produce new eczema in a patient who already has eczema is a great deal less than that which will produce urticaria or respiratory symptoms in a patient who has respiratory allergy alone. Why is this?

It seems clear that there is some predisposing condition in the skin, immunologic or otherwise, in persons with atopic dermatitis, which is not present in those who have hay fever alone, although they both give identical wheal type scratch tests. It is likely that this condition, whatever it may be, *in combination with the urticarial type sensitivity,* is responsible for the production of dermatitis, and that atopic dermatitis is not produced without it. Let us call this the X-factor.

3. If I sensitize a small place on my own skin with an egg white reagin containing serum from an eczematous baby, and then eat an egg, or indeed sometimes only an infinitesimal amount of egg white, in about twenty minutes an urticarial wheal appears on the sensitized site—never eczema. If every day I eat small amounts of egg white below the amount necessary to produce urticaria, no eczema ever develops. It is either immediate urticaria or nothing: there is no cumulative reaction. I cannot produce eczema on myself by eating a food to which my skin is sensitized, no matter in what amount I eat it. I can produce only urticaria, presumably because the X-factor is not there.

4. It is true that many times people with atopic dermatitis can eat the foods which give positive skin tests with impunity, so that these tests are often entirely without etiological significance. In Louis Tuft's well-known "dust patient,"[12] there were positive intracutaneous tests to twenty-seven different foods, and yet his eczema was proved to be entirely due to house dust, and had nothing

[12]Tuft, Louis, Tuft, Harold S., and Heck, V. Muriel: Atopic Dermatitis, an Experimental Clinical Study of the Role of Inhalant Allergens, J. Allergy **21**: 181, 1950.

whatever to do with the foods to which he gave positive tests. This is a classical paper, and everyone seriously interested in atopic dermatitis should read it.

In spite of these objections which I have enumerated there can be no doubt that *sometimes* positive scratch or intracutaneous tests indicate etiology, and are of great value in planning treatment. I think that almost all allergists would agree to this, and possibly an occasional dermatologist.

Is it possible to reconcile these somewhat contradictory observations? I think it may be. The following hypothesis, which seems to me to follow logically from the observed facts, is suggested. The wheal test reaction is of no significance in atopic dermatitis by itself; it is significant only if it is accompanied by another factor, the X-factor. I have no idea whatever what this added factor may be. *The wheal reaction is, however, sometimes indicative of etiology because it is sometimes accompanied by the X-factor.* By itself it is of no moment so far as eczema is concerned.

It was shown a good many years ago by Oscar Schloss,[13] who was in his day the foremost research pediatrist in America, and who has been rarely equalled and never surpassed, that a new food when introduced into the diet of a young infant is often followed by the development of a positive skin test. This is a normal phenomenon. The degree of sensitivity is never high, and the positive test lasts for only a short time. Later Brunner and Walzer[14] showed that even in older children and adults the passage of unsplit food protein through the gastrointestinal mucosa and thence to the blood is a normal phenomenon. In atopic people this circulating protein sensitizes the skin more readily than it does in the normal person, and the positive skin tests which result are of much greater degree and last longer, sometimes for many years (fish, nuts). The same is true of environmental allergens, which reach the blood by inhalation. Many of these positive tests, particularly those to foods, may be looked upon as normal for the atopic person and have nothing to do with his symptoms, whether they be those of eczema, hay fever, or asthma.

I think the main reasons for this are two:

A. The X-factor is not present; therefore eczema is not produced.

B. The degree of tissue sensitization is not high enough to react with the amount of antigen absorbed.

The immunologic reaction we are discussing depends upon two variables:

(1) The amount of antibody fixed in the tissue.

(2) The amount of antigen which contacts it.

If there is a small amount of antibody it takes a large amount of antigen to produce a reaction, and vice versa.

Several years ago I did some immunologic experiments on myself with the help of Miss Margaret Scully who was in charge of the allergy laboratory of the Children's Hospital at that time. It is not necessary to go into the details of these investigations. The gist of them was that if

[13] Schloss, Oscar: The Intestinal Absorption of Antigenic Protein, The Harvey Lectures, p. 156, 1924-1925.

[14] Brunner, Matthew, and Walzer, Matthew: Absorption of Undigested Protein in Human Beings, Arch. Int. Med. 42: 172, 1928.

a high degree of passive sensitization was produced on my skin by the intracutaneous injection of a serum containing food reagins from an eczematous infant, the eating of the corresponding food in only small amount caused a wheal to appear on the sensitized site in about twenty minutes. We studied egg white, chicken, peanut, wheat, and potato. If the degree of sensitization was only moderate or slight, as determined by serial titration of the sites, no reaction would take place, either urticarial or eczematous, even if the food were eaten in large amounts. This simple principle applies to any tissue as well as to the skin, and seems to me of fundamental importance in clinical allergy.

Skin Testing.—Skin testing is often a valuable procedure in atopic dermatitis as a help in planning treatment. Its value has, however, been greatly exaggerated, too much attention has been paid to it, and harm has been done, particularly in babies and in young children by too rigorous dieting solely on the basis of skin tests. What the mother has actually seen happen to the child is more important. Skin testing is a laboratory procedure, and like all other laboratory procedures it must be evaluated in relation to the patient and not by itself.

Too much attention to laboratory tests and too little attention to the patient is one of the defects of modern medicine, and is often carried to an absurdity. I saw not long ago a bottle-fed eczematous baby 7 months old whose family had moved to Boston from a large midwestern city. The mother brought with her a typed report of the skin tests that had been done there in a thriving private clinic. Eighty tests had been done by the indirect method, forty-six of which were reported positive. Some of the things tested for were tobacco, camel hair, mustard, cinnamon, allspice, ginger, paprika, garlic, vanilla, strawberry, and cucumber. This is not an isolated example by any means.

When one sees such things he begins to believe that there is as much foolishness in modern medicine as there was in the time of William Shakespeare, and he is not far from right.

There is no need of doing a large number of skin tests on a baby with eczema. If he is tested with most of the foods he is eating, plus egg white, and with a few of the environmental allergens to which he is exposed, that is enough. I never do an intracutaneous test until a scratch test has been done first and is negative, and would not do an intracutaneous test with egg white on any baby, no matter what the scratch test showed. It is sometimes desirable to do a few intracutaneous tests with other allergens on eczematous babies, as the skin sensitivity is often of low degree and the intracutaneous test may be positive when the scratch test is negative. I have not used the indirect method of testing for over ten years except for investigative work—it is more bother than it is worth. This could be discussed at considerable length—I will simply say that I do not think much of it. As a matter of fact, it is possible to treat most babies who have atopic dermatitis very well without doing any skin tests at all. I find myself doing fewer and fewer, and the patients seem to do about as well as when I was careful to do complete testing on every patient. Older children, whose

trouble is likely to be coming from the environmental allergens, particularly pollen and dust, can be understood better and treated better if pretty complete testing with the environmental allergens is done.

In a series of 100 eczematous babies under 1 year of age, who gave positive scratch tests to something, the positive tests to foods were as follows:

Egg white	86	Corn	2
Milk	26	Spinach	2
Wheat	17	Pea	2
Oat	8	Carrott	2
Barley	6	Orange	2
Beef	6	Lamb	2
Potato	4	Codfish	1
Haddock	3	Chicken	1
Tomato	3		

Fifty-six gave positive tests to something they were eating, thirty-nine gave positive tests to egg white alone. It must be understood that this series of 100 was not made up of consecutive cases—they were all babies with atopic dermatitis who reacted to something; no babies who had negative skin tests were included.

In a series of thirty-eight under 1 year of age, tested by the scratch method with fifteen environmental allergens, only four children gave positive reactions—the allergens were silk, cat hair, and wool. However, in a series of forty-four which had negative scratch tests to dust and feathers, thirty-one had positive intracutaneous tests to dust and twenty-five to feathers. At the time these tests were made the high percentage of positive reactions was surprising to me, and still is. It may be that some of these were irritative reactions, as fairly strong testing solutions were used, but they gave no reactions on normal babies, and in a good many of these babies reagins for dust and for feathers were present as well as positive skin tests.

In older children positive scratch tests to a variety of environmental allergens become more frequent. In a large series the ratio between positive reactions to foods and to environmental allergens was 2.5 to 1, in a series of infants under the age of 1 year it was as 20 to 1.

The Egg White Reaction.—The egg white reaction is so important in the atopic dermatitis of infants that it warrants special discussion. It has been found (Moro, Woringer, Hill) that most infants who have atopic dermatitis give strongly positive skin reactions to egg white, the majority of which are accompanied by circulating reagins and clinical sensitivity. Many of these babies are so exquisitely sensitive to egg white that the ingestion of only minute amounts is followed by stormy symptoms (urticaria, vomiting, shock). Horesh[15] has pointed out, and with truth, that even the smell of egg white may cause symptoms, and that eczematous babies who are sensitive to it should be kept out of the kitchen when eggs are being broken for use in cooking. This is entirely right. Egg sensitivity lasts a long time, sometimes well into childhood. I have no accurate figures, but I doubt that it often lasts into adult life, and even in childhood its frequency is considerably diminished from what it is in infancy. It is a curious fact that in infants who have asthma, the egg white reaction is uncommon, unless the asthma is accompanied by eczema. The egg white reaction apparently has to do particularly with eczema. In a series of 100 asthmatic

[15]Horesh, A. J.: Allergy to Food Odors, J. Allergy **14**: 335, 1943.

children, about half of whom had had eczema in infancy, twenty-one gave positive scratch tests to egg white, but only eleven were clinically sensitive to it.

A positive scratch test to egg white is of some value in differential diagnosis, for the chances are that if it is absent, what the baby has is not atopic dermatitis. This, however, is by no means certain, for some babies with atopic dermatitis give negative egg tests. I think the absence of a positive reaction is probably also of some prognostic value, and that one is justified in telling the mothers of such patients that the child is certainly not a highly allergic child, and that he has better than an even chance of escaping hay fever and asthma.

The direct influence of egg white in causing eczema in young babies is not great, for most mothers and doctors know enough now to keep it away from allergic babies. It is in this respect somewhat more important in older children whose diet is not so well controlled, and who may be eating enough egg-containing food to get into trouble.

While the actual eating of egg white is of little importance as a cause of eczema in most infants, I have a suspicion that the *fact* of egg sensitization may be of considerable importance. This is the primary sensitization for most of these infants. It is a sensitization of high degree, much more so than most of the others which follow it, and it has been thought, particularly by Moro, with whom I agree, that such sensitization, once it has taken place, makes the individual more susceptible to other sensitizations. It puts the stamp of allergy upon him—once he has become egg sensitive he has been admitted to the allergic fraternity, and is likely to continue his membership for a long time.

A good many years ago, Bret Ratner,[16] after some painstaking laboratory work and considerable clinical observation, came to the conclusion that sensitization to egg white as it occurs in infants, and sometimes to other potent allergens such as fish and nuts, is congenital, and due to placental transmission of the allergen. This is *active* sensitization. I have always agreed with this. I do not see how it could take place in any other way, as most of these babies have never even seen an egg, let alone eating it. Some very competent allergists and immunologists have, however, disagreed, largely because positive skin tests to egg white are rarely obtained in newborn infants. One serious defect of these observations is that in order to arrive at any worth-while conclusions these tests should be done on a large series of infants whose mothers or fathers have hay fever—this has never been done. Testing the infants of normal mothers and fathers means but little, for it is largely the children of parents with hay fever who have eczema, and not so often those of normal parents.

It is true that often a baby, when tested at the second or third month, will have a negative egg white test, and when tested again at the sixth or seventh month it may be strongly positive in spite of the fact that he has not come into contact with egg during the intervening months. It is also often true that just about the

[16]Ratner, Bret: A Possible Causal Factor of Food Allergy in Certain Infants, Am. J. Dis. Child. 36: 277, 1928.

time the egg white test becomes positive an eczema which has previously not amounted to much may turn into a very severe one, even to the erythrodermic point.

These are the facts—the explanation is obscure. I think in the last year some light may have been shed on it. The young baby does not make gamma globulin as a rule until he is about 4 to 12 weeks old.[17] What he has of it before this he has obtained from his mother. Until he can make his own gamma globulin he does not begin to make egg white antibodies, and until he does this he does not have a positive skin test to egg white. The weak point of this theory is that he has had no contact with the antigen since he was in utero. It is not known how long egg antigen may persist in the body, but it is well known that other protein antigens may persist for several months.

Sensitivity to egg white is such a common and such a striking phenomenon in infants with eczema, it is so much greater in degree than the other sensitizations which exist, and I have seen so many babies with a high degree of egg white sensitivity in whom no other sensitivity could be demonstrated that I have always had a suspicion that it may have something to do with the eczema even if there is no contact with the antigen (egg white). This is, of course, immunologic heresy, and I have no idea whatever how it might work.

REGULATION OF THE DIET

Many positive skin tests to foods are of no etiological significance. This is not so likely to be true for babies as for older children. It is probably best in dealing with babies to omit those foods which have given well-marked positive scratch tests, provided there are not too many of them, and see what happens. With moderation, and the admixture of a good measure of commonsense, the same is true for older children. I will say again that no infant or child should be placed upon a poorly balanced or insufficient diet, no matter what the skin tests show. If there is going to be improvement from the removal of a food, this will not take place at once, because the skin has been damaged, and it will not return to normal in a hurry, no matter what is done. If there is not decided improvement at the end of two weeks, it is fair to conclude that the food in question has nothing to do with the eczema. If there is considerable improvement, and several foods have been removed, so that there is doubt as to which are the important ones, one food at a time over three-day periods is added, and results noted.

An almost routine basic diet which I use in dealing with atopic dermatitis is as follows:

Rice	Bananas
Lamb	Applesauce
Milk (or sometimes soybean food)	Apricots
	Pears
Carrots	Peaches
String beans	Jell-o
Squash	Vi-Penta drops
Potato (for older children)	

This is a well-balanced diet, and a baby can stay on it for a long time. Most babies will eat the same thing day after day. They do not need a large variety of foods, no matter what the mother thinks about it, and the present fad of feeding fifty-seven different varieties of foods to very

[17] Dr. David Gitlin, Immunology Laboratory, Children's Medical Center, Boston. Personal communication.

young babies, to my mind has no sense to it, although I am sorry that I cannot say truthfully that I have seen it do much harm, except to some allergic babies. All allergic babies with symptoms of any sort referable to allergy should be on a simple diet containing relatively few foods.

SPECIAL FOODS

A few foods are important enough to deserve special discussion.

Milk.—Milk contains four proteins: lactalbumin, casein, lactoglobulin, and opalisin. Opalisin exists only in traces, lactoglobulin in very small amounts; it is probable that they are of little or no importance in allergy. Lactalbumin and casein are the important ones, and of these lactalbumin is by far the more important. Sensitivity to casein exists, but it not so common as sensitivity to lactalbumin, as casein is coagulated in the stomach and is not readily absorbed before digestion, while lactalbumin is a soluble protein, and is therefore more easily absorbed in antigenic form.

In 153 eczematous infants under 1 year of age, from my old records, there were seventeen positive scratch tests to either lactalbumin or casein or to both. Most were to both proteins, but as it is impossible to obtain a casein preparation which is entirely free of lactalbumin, the authenticity of some of the casein reactions is open to doubt. In a series of sixty-three infants who had negative scratch tests to lactalbumin, about 50 per cent gave positive intracutaneous tests. It has seemed to me that positive scratch tests to milk are almost always of etiological importance in infantile eczema — positive intracutaneous tests sometimes are. In eczema the sensitivity to milk is not of high degree; if it were it would not be possible for the infant to take any milk without violent symptoms, and still he drinks a quart a day with no adverse symptoms except perhaps a bit of colic, and thrives except for his eczema. I think that at the present time altogether too concentrated milk mixtures are being fed to too young babies, and that this is partly responsible for the increase in eczema and other allergic symptoms. I see not a few babies who are taking as much as 3 ounces of whole milk per pound of weight per day. This represents an enormous intake of protein for such a small creature. It is not a bad idea, although it may be difficult with some hungry babies, to stick to the old rule of 1½ to 2 ounces of whole milk or its equivalent per pound per day.

If the skin test to milk is positive it is best to remove milk from the diet and to substitute one of the milk-free foods. Sobee, Mull-Soy, Soyolac, and Nutramigen are at present the most popular. The first three are made from soybean flour with the addition of various fats, carbohydrates, salts, and vitamins. The base of Nutramigen consists of amino acids which have been derived from the breaking down of casein. Fat, carbohydrate, salts, and vitamins have been added. All are excellent preparations, and will nourish a baby as well as milk, even over long periods of time. The trouble is that the soybean preparations are altogether too likely to cause diarrhea and sore buttocks; the younger the baby the more often this happens. It is said that the new liquid Sobee is less likely to do this than the others. I cannot vouch for this from personal experience—I have used too little of

it. I think Nutramigen is the best to use for babies under 3 months. The stools with Nutramigen are of thin consistency, as it has little residue, but there is rarely actual diarrhea. The trouble with Nutramigen is that it has a very strong taste, somewhat resembling beef tea, and babies tire of it more easily than they do of the soybean foods. I have seen one child, however, who was fed on it for over two years.

I said twenty years ago that I thought sensitivity to milk was probably the most common single cause of atopic dermatitis in infants. However, most of the eczematous babies that are now brought to me have been on some milk-free food for a considerable period with no benefit whatever. I see, for the most part, only those for whom a milk-free diet does no good, and for a while I had the thought that perhaps my original ideas about milk sensitivity in eczema were wrong. My pediatric friends assure me, however, that this is not so, and that, due to extensive advertising, most pediatricians now use these foods so much that I see, as a consultant, only those in whom they do not work. This may be so.

Whether it is so or not, I am entirely sure that the milk-free foods are being used altogether too much, and, for the most part, without a great deal of intelligence, and that the frequency of milk sensitivity of every sort (gastrointestinal, respiratory, etc.) is being exaggerated; like every good thing it is being worked to death. The tendency is now, on account of superadvertising of the soybean foods, for pediatricians to put every baby they see with any sort of skin rash, from ammonia dermatitis to flea bites, scabies, and often what is obviously contact dermatitis, on a milk-free diet at once. This is not only stupid, but may do harm if the baby develops a severe diarrhea. The milk-free foods are of great value when used properly, and they have been a boon to many babies, but when Harold Stuart and I[18] introduced Sobee in 1929, we started something that has gone too far.

Goat's milk can sometimes be used to great advantage in some forms of milk sensitivity, particularly for patients with gastrointestinal allergy and for almost all of those babies who are so violently sensitive that they go into shock from the ingestion of only a few drops of cow's milk.[19] Although an occasional infant with eczema due to cow's milk is relieved or even cured by the use of goat's milk, this does not happen often because the caseins of goat's and cow's milk are identical immunologically and chemically, and while the two lactalbumins are somewhat different immunologically, they are by no means entirely species specific; there are many crossed reactions. Some years ago I tested forty-four eczematous infants who had given positive intracutaneous tests to cow lactalbumin, with a specially purified preparation of goat lactalbumin. There were twenty-five positive reactions. Why it is that goat's milk is so often tolerated by infants who have severe shocklike symptoms from cow's milk and is only occasionally of use in

[18] Hill, Lewis, W., and Stuart, Harold C.: A Soybean Food Preparation for Feeding Infants With Milk Idiosyncrasy, J. A. M. A. 93: 985, 1929.

[19] Hill, Lewis W.: Immunologic Relationship Between Cow's Milk and Goat's Milk, J. PEDIAT. 15: 157, 1939.

eczema due to cow's milk, I do not know. I suspect that the antibodies in the two conditions may be different, and that the antibody in the patients with eczema is less specific than the antibody in those with shocklike symptoms.

Foods Eaten by the Cow as a Cause of Eczema.—It has been said that eczema may be due to sensitivity to foods eaten by the cow—particularly

tests to corn, and one to alfalfa—no positive tests to any of the others.

Egg White.—Egg white should be kept out of the diet of all these babies, unless there is a definitely negative scratch test to it, and it is best to do this two or three times before giving the baby egg. Hard-boiled egg yolk is usually tolerated; soft-boiled egg yolk should not be given, as it is not possible to separate

Fig. 23.—This papular eruption was entirely due to the ingestion of wheat. There was no eczema on any other part of the body. It can be compared to a fixed drug eruption.

linseed or cottonseed. I see no reason why this should not be so. However, I have never seen a patient in whom I thought it was so, and once I tested a series of forty-three eczematous babies under 1 year of age with cottonseed, linseed, soybean, corn and alfalfa, all foods which are used in the standard diet of many dairies. There were three slightly positive

it entirely from the white. Furthermore, the baby should be kept out of the kitchen when the mother is breaking or cooking eggs (except boiled eggs). It is almost incredible what a minute amount of egg white can cause a reaction. I once had my arm sensitized with a strong egg serum, and ate a piece of bread that had a little shiny glaze of egg white on the

crust: in twenty minutes a wheal developed on the sensitized site.

Wheat.—Wheat sensitivity is important in many eczematous babies, and in not a few older children. A positive scratch test is usually significant. Wheat is not easy to deal with, for the year-old child is a great cracker eater, and the older child depends so much on all sorts of wheat-containing foods. It is important to explain to the mother exactly what wheat flour is, and what articles of diet contain it. This statement may sound superfluous, but it is by no means so. Some women do not even know that bread is made of wheat, others think that the only wheat-containing bread is whole wheat bread, many women do not know that graham crackers are made from wheat, and so on ad nauseam. For babies the "Happy Tappy"* crackers are excellent. They contain tapioca flour, apple juice, and dried milk. The trouble with them is that they are no good for babies who are sensitive to milk as well as to wheat. "Ry-Krisp"† wafers serve the same purpose. They are swallowed better if they are spread with butter and apple jelly. Practically all rye breads contain wheat. For the older child, the mother can learn to make corn cake, biscuits from rice flour, or sweetened cookies from either of these or from soybean flour. I have been trying for years to induce one of the largest manufacturers of infant foods to supply sweetened crackers made from rice, oat, barley, and corn flour, with no luck at all. There is need for such crackers.

Tomato Juice.—Tomato should never be given to any child with atopic dermatitis. Skin tests to tomato are uncommon, but for some unknown reason it produces skin rashes with great frequency, possibly due to the pigment it contains, possibly due to whatever it is that gives it its characteristic taste.

Orange Juice.—It is common for the mother to notice that the baby "breaks out" if orange juice is given. It is probably best to remove it from the diet of all infants who have atopic dermatitis, for orange juice is of little or no value to a baby except as an antiscorbutic, and if he is taking any "multivitamin" drops he is getting an adequate amount of vitamin C. If he is not, it is a simple matter to give him some ascorbic acid.

Positive scratch tests to orange are uncommon: in 300 cases there were only four. In a series of twenty-three tested by the intracutaneous method, however, there were eight slightly positive tests. Sensitivity to orange is almost always of low degree—I have seen one 4-year-old child, however, who was exquisitely sensitive to it, and who had an enormous positive scratch test.

There are in orange juice three substances which may produce allergic symptoms:

1. The protein of the juice
2. The protein of the seed
3. The peel oil

The relative importance of these is not entirely clear. In most commercially prepared orange juice there is plenty of chance for peel oil and seed protein to be present. Bib* canned orange juice contains no seed protein and no peel oil, and in five infants who had allergic symptoms from ordinary orange juice, Ratner and his co-

*Maltex Co., Burlington, Vt.
†Ralston Purina Co., St. Louis, Mo.

*Bib Corporation, Lakeland, Fla.

workers[20] found that the Bib juice was tolerated. They do not say what sort of allergic symptoms were present. I have had no personal experience with it.

In orange juice, as it is prepared at home, it is not likely that any seed protein is present, and the amount of peel oil must be very small, although possibly enough to produce symptoms. The oil of orange peel in addition to being a sensitizer (its active principle is dextrolimonene, which is closely allied to turpentine) is a primary irritant, and dermatitis of the fingers from it has been known for a long time and is common in adults whose work involves the cutting up of oranges. It seems likely that if sensitivity to orange peel oil existed in infants it would be epidermal rather than dermal, and would therefore not be demonstrated by scratch or intracutaneous tests. Sensitivity to the juice protein or to the seed protein is shown by urticarial type scratch or intracutaneous tests.

Ratner and his co-workers[20] in a painstaking study showed clearly that the protein of orange juice is not readily absorbed from the digestive tract in an unsplit antigenic condition, and said, "What we call allergy to citrus fruit may in truth not be allergy in all instances, but irritation from the peel." This seems likely.

(To be concluded.)

[20]Ratner, Bret, Untracht, Samuel, Malone H. John, and Retsina, Mary: Allergenicity of Orange Studied in Man, J. PEDIAT. 43: 421, 1953.

Medical Progress

RECTAL BLEEDING IN INFANTS AND CHILDREN

With A Hitherto Unreported Etiological Factor

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RECTAL bleeding, as a presenting or concomitant complaint in childhood, occurs frequently enough to be a cause of anxiety to the family and the physician. A small percentage of such children have serious pathology, of which bleeding is the signal, but the majority have only a disturbing sign. However, in order to differentiate between the serious and the transient bleeder, a more or less standard routine should be followed in searching out the etiological factor. This has been done at the Children's Hospital of Philadelphia where we have had the opportunity to see primarily, or in consultation, a series of 143 cases of melena over a four-year period. These will be used as the basis for this report. We shall record and discuss possible causes for the bleeding, suggest an investigative program for etiological factors, and outline the results of a follow-up on these 143 cases.

In the course of studying children with rectal bleeding, we have encountered a clinical entity which undoubtedly has been noted by others, but, so far as we can determine, has not been reported in the literature. We have called this condition "chronic recurrent intussusception of the sigmoid colon," and it will be described in some detail under possible causes.

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HISTORY

When the patient is first seen for the complaint of rectal bleeding, one would like the parents to answer at least six basic questions in order to evaluate the problem:

1. What quantity of blood has been passed?
2. How long has it been going on?
3. What color is the blood, bright or dark?
4. Is the blood on the surface of the stool or mixed intimately in the stool?
5. Is the blood passed before or during the bowel movement?
6. Has the child had any associated signs or symptoms such as abdominal pain, nausea, vomiting, cramps or shock?

With the answers to these questions, one can begin systematically to think through the possible causes of the melena. The quantity of blood lost and the length of time it has been going on are important to know in judging the acute or chronic nature of the problem. The color of the blood and its location on the stool will give a lead as to whether the cause is low in the intestine or higher up. The associated signs of peritoneal irritation are important in judging the innocence or severity of the underlying cause.

CAUSES OF MELENA

Possible causes are summarized anatomically in Fig. 1. A diagrammatic scheme of the same causes is shown in Table I. At the risk of oversimplification, an attempt is made to group the causes so as to show those most commonly exhibiting dark blood in the stool, indicating generally a high intestinal cause, and those showing bright blood, usually indicative of a low intestinal cause. Some of the pathological lesions which generally give dark blood, because they are in the small intestine, can also give bright bleeding if the blood loss is brisk and peristalsis hyperactive. In addition, some of the etiological factors are accompanied by pain as part of the clinical picture; these are also grouped in the schematic representation.

The causes will not be considered in order of their importance or frequency, but they will be discussed in descending order from the mouth to the anus.

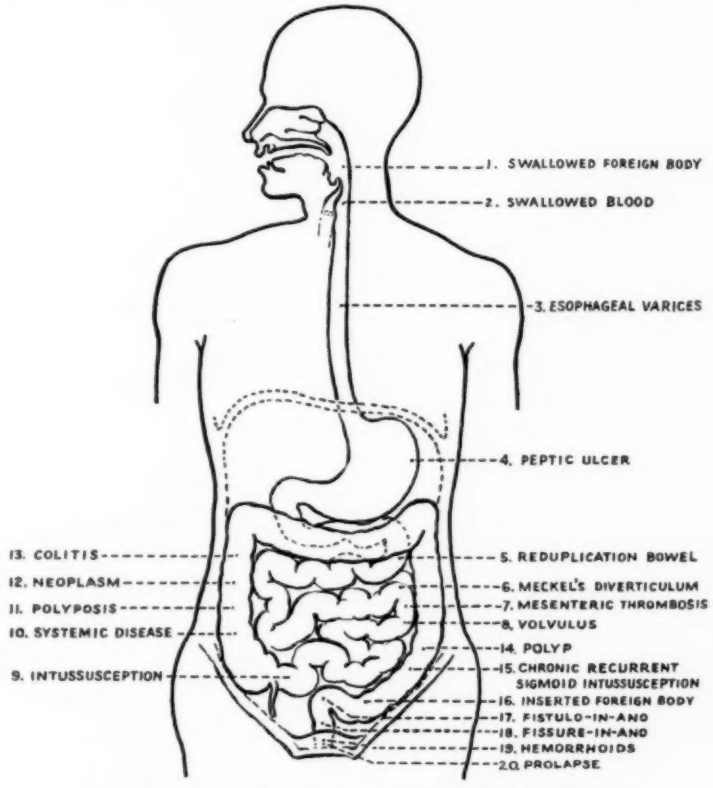

Fig. 1.—Anatomical location of causes for rectal bleeding.

Table II summarizes these facts. A brief word on therapy will be included under each etiological factor.

1. Swallowed Foreign Body.—This is a rare cause of blood in the stool, although often considered by the laity as one of the most common causes. When it does occur, the history of ingestion of a foreign body can usually

be elicited. Trauma can occur anywhere in the gastrointestinal tract and when it does cause bleeding, the blood loss most commonly is small in amount and dark. It is intimately associated with the stool and without peritoneal signs unless the trauma has caused perforation of the bowel. In this latter case rectal bleeding will probably not be the presenting complaint.

TABLE I. DIAGRAMMATIC OUTLINE OF RECTAL BLEEDING CAUSES IN CHILDHOOD

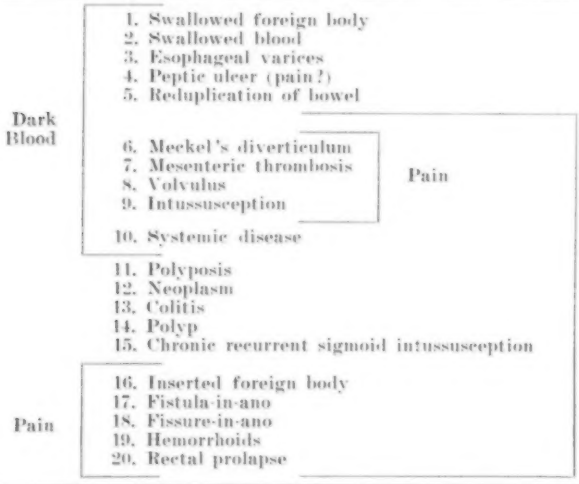

TABLE II. SUMMARY OF CHARACTERISTICS OF RECTAL BLEEDING FROM VARIOUS SOURCES

CAUSES	COLOR		POSITION IN RESPECT TO BOWEL MOVEMENTS		AMOUNT		TIME IN RESPECT TO BOWEL MOVEMENTS			PAIN AND/OR PERITONEAL SIGNS
	BRIGHT	DARK	ON	IN	SMALL	LARGE	BEFORE	DURING	AFTER	
1. Swallowed foreign body		C		C	C			C		N
2. Swallowed blood		C		C	C	O		C		N
3. Esophageal varices	O	C	O	C	C	O		C	O	O
4. Peptic ulcer	O	C	O	C	C	O		C	O	O
5. Reduplication of bowel	O	C	O	C	C	O		C	O	N
6. Meckel's diverticulum	C or	C	C or	C	C	O	O	C	O	N
7. Mesenteric thrombosis	C or	C	C or	C	C		O	C	O	C
8. Volvulus	C or	C	C or	C	C		O	C	O	C
9. Intussusception	C or	C	C or	C	C	O	O	C	O	C
10. Systemic disease	C or	C	C or	C	C			C		N
11. Polyposis	C		C or	C	C	O		C	O	N
12. Neoplasm	C		C		C			C		N
13. Colitis	C	O	C		C or	C		C	O	C
14. Polyp	C		C		C or	C		C	O	N
15. Chronic sigmoid intussusception	C		C		C			C		N
16. Inserted foreign body	C		C		C		C			C
17. Fistula-in-ano	C		C		C			C or	C	C
18. Fissure-in-ano	C		C		C			C or	C	C
19. Hemorrhoids	C		C		C			C		C
20. Rectal prolapse	C		C		C		O	C or	C	C

C—Commonly.
N—Not usual.
O—Occasionally.

Watchful waiting is indicated here, unless signs of perforation supervene or the object is not passed per rectum. Surgical intervention may then become necessary.

2. Swallowed Blood.—Any diagnostic or therapeutic procedure carried out in the nose, throat, esophagus, or stomach may result in blood appearing in the stools. Laryngoscopy, a traumatic endotracheal intubation, esophagoscopy or breast feeding from a fissured nipple under certain circumstances may result in ingestion of blood which would secondarily be manifested in the stools. More commonly, epistaxis or operative procedures in the oropharynx will be the cause for swallowed blood. In all of these, the stool blood arouses less concern because of the history. The stools will usually contain dark blood, in small amounts, mixed with the feces, occurring during a bowel movement and without other abdominal signs.

Symptomatic therapy alone is indicated for this.

3. Esophageal Varices.—This is a variable etiological factor. The varices may give no or insignificant melena, or they may be productive of the picture of exsanguination. In the former case, the blood is dark, in the stool, and small in amount. In the latter type, brighter blood will be seen in large amounts, during and after stooling and accompanied with signs of shock. In either case, signs of portal obstruction, e.g., hepatomegaly and/or splenomegaly, collateral circulation, ascites, etc., are helpful in suggesting the basic diagnosis.

Medical management of the cause for varices must be undertaken and consideration given to a surgical procedure designed to relieve portal hypertension.

4. Peptic Ulcer.—This condition, so prevalent in adults, is infrequently seen in children, but it must be included as a possibility in childhood rectal bleeding. If it is the cause, the bowel movement will usually contain a small amount of dark blood accompanied by variable and inconstant pain and minor peritoneal signs. One must bear in mind, as a remote possibility, the presence of an intracranial lesion causing the peptic ulcer—the so-called Cushing ulcer.

Medical treatment for the ulcer is usually effective.

5. Duplication of the Bowel.—Although duplication of the gastrointestinal tract can occur at any point in its length, the small intestine seems to be the site of predilection. Included in the contents of the mucosal lining of such duplications are aberrant cells. There may be gastric glands, pancreatic tissue or any other type of gastrointestinal cell found in the duplication. The secretion from these cells may digest the mucosa along its margins so as to cause bleeding. When it occurs, which is rare because duplications are rare, the blood is usually dark in color, small in amount, part of the stool, occurring with the stool, and without other signs except the presence of a mass.

Elective surgical removal constitutes desirable treatment unless exsanguination occurs, when emergency laparotomy is indicated.

6. Meckel's Diverticulum.—All that has been said about duplication and aberrant gastric or pancreatic cells is likewise true for Meckel's diverticulum. Yet, because this congenital remnant is found much more commonly than duplication, it should be higher on the list of suspected causes for rectal bleeding. The bleeding may be bright

or dark, depending on the degree of hemorrhage; it may be in or on the stool; it is usually small in amount but can be massive; blood loss generally comes during stooling but may be an evacuation itself; and it is generally without peritoneal signs unless of an exsanguinating variety. Inflammation or fistula formation in a Meckel's diverticulum does not usually cause bleeding.

If Meckel's diverticulum is suspected as a cause for the bleeding, exploratory laparotomy should be undertaken immediately because of the frequency with which such a bleeding diverticulum is the cause of exsanguination.

7, 8, and 9. Mesenteric Thrombosis, Volvulus, and Intussusception.—These are three mid-intestinal lesions which have pain as one of their outstanding symptoms and are usually seen by the pediatrician for this rather than for the bleeding, which is a concomitant finding. Since the clinical picture and bleeding characteristics are generally the same in all three, we will deal with them together. In each case, blood appears in the gastrointestinal tract as a result of compromise to the vascular supply of the bowel. In thrombosis, it is a clot from a distant or local source, or a lesion causing stasis in mesenteric vessels. In volvulus, a mechanical twisting of the mesentery so as to shut off the vascular channels produces the pain and bleeding; however, bleeding is a bit less constant in this than in the other two because all of the blood may be trapped in the twisted loops and not find its way to the anal orifice. In intussusception, the leading point will have its blood supply embarrassed and frequently cause blood to appear in the rectum. A mass and colic, if present, are helpful in differentiating this from other causes. As stated previously, all three of these generally have signs of abdominal pain, and sometimes of parietal peritoneal irritation predominating, and the bloody stool is merely corollary evidence of the difficulty. These entities have dark or bright blood, in large or small amounts (usually the latter), and the bleeding may occur at the time of stooling or separately.

All three of these conditions require immediate surgical intervention, not so much to relieve the bleeding as to correct the bowel lesion which has compromised the circulation.

10. Systemic Disease.—The almost numberless medical entities that can give rectal bleeding as one of their manifestations should be considered in any differential diagnosis, but these seldom give melena as the presenting complaint. They can generally be ruled in or out by other evidence, but they must at least be borne in mind by the examiner. A few of the commoner systemic disease causes are listed for the sake of completeness, e.g., hypovitaminosis, hemorrhagic disease of the newborn, leukemia, purpura, allergy to milk and other foods, syphilis, and parasitic infestation. Liver disease, especially that associated with a fibrinogenemia and hypoprothrombinemia, can also give melena. All of these, when rectal bleeding is present, are usually characterized by a small amount of blood, which may be dark or light, mixed or on the stool, occurring during bowel movement, and usually without peritoneal signs.

All of these conditions require medical management as opposed to surgical therapy, although, at times, exploratory laparotomy is undertaken because of frank hemorrhage and the difficulty of making the nonsurgical diagnosis.

11. Polyposis.—It is well known that this is often a familial disease and therefore may be suspected from history alone as a cause for bleeding from the rectum. The danger of malignant degeneration is far greater than the bleeding danger. The condition is fairly easy of diagnosis by proctoscopic examination and/or x-ray examination, if it is considered among the possibilities. When present, the blood is generally bright, on the stool, small in amount, occurring with the stool, and without peritoneal signs.

In true polyposis, because of the risk of malignancy, elective colectomy is most often mandatory.

12. Malignant Neoplasm.—No differential diagnosis of rectal bleeding would be complete without considering neoplastic disease. Malignant tumors are relatively rare in the gastrointestinal tract in children, though they are a possibility, especially in the large bowel. Roentgen examination and proctoscopy will usually be helpful in establishing the diagnosis. The bleeding, when present, is usually bright, small in amount, on the stool when it is passed, and generally without peritoneal signs.

When there is any indication that a neoplasm has caused the bleeding, laparotomy must be undertaken at the earliest possible date.

13. Colitis.—Amebic and ulcerative colitis are relatively rare entities in childhood and should merely be mentioned in passing for the sake of completeness. Nonspecific or so-called viral colitis, too, can produce melena, but the accompanying systemic symptomatology usually is sufficient to make this diagnosis. Bleeding from the rectum is only a minor consideration in the over-all picture of all three of these.

The problem of colitis should not be left without mention of the allergic colitis seen occasionally in infancy. Allergy to milk is uncommon, and, in addition to bright red melena, it is usually accompanied by colicky pain. A proctoscopic examination shows a congested and hypertrophic mucosa which bleeds on the slightest trauma.

Medical management of these causes is indicated, with surgical ileostomy and colectomy reserved for the severe case.

14. Polyps.—This entity is distinguished from the familial variety mentioned above because it is one of the commonest causes of melena. These polyps are usually single, or two or three in number, and can frequently be felt by rectal examination. They can bleed profusely at times, even to the point of exsanguination, although this is a rare circumstance. Because of their low position, the blood is usually bright and on the outside of the stool. Blood may be passed alone without feces and can be squirting in character, and seldom is the bleeding accompanied by peritoneal signs. Rarely, the polyp itself will be passed per rectum.

Surgical removal must be undertaken either through the proctoscope, if low enough, or by colotomy if higher.

15. Chronic Recurrent Sigmoid Intussusception.—Early in the course of examining infants and children with the proctoscope for rectal bleeding, we became aware that the physiological redundancy usually seen was sometimes exaggerated. When a normal child would strain or cry, the upper sigmoid would intussuscept downward against the end of the scope and obliterate our view. Air insufflation would push it back, but it would promptly come down again. After several such

episodes in the same examination, the leading point of the intussusceptum began to bleed. Very shortly thereafter, while examining another child, this reddened, bleeding intussusceptum presented itself when the scope was first passed. Over the course of the past few years many examinations have been made, and this bleeding, ulcerated leading point had been noted on at least eighteen occasions in a series of 143 rectal bleeders. In the absence of other demonstrable cause

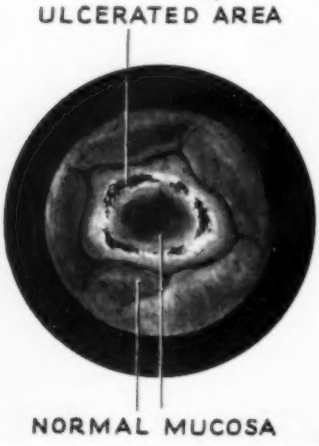

Fig. 2.—Drawing of chronic recurrent sigmoid intussusception as seen through adult proctoscope.

for the melena, it has been incriminated as the etiological factor. The intussusceptum becomes ulcerated, edematous, and bleeds when a chronically constipated child repeatedly strains at stool and the leading point is traumatized against the hard fecal mass. The bleeding, when due to this cause, is usually bright, on the stool, small in amount, and without peritoneal signs. Fig. 2 is a drawing of what is seen through a proctoscope in this condition. It is well to note also that this entity will be missed unless an adult-sized proctoscope is employed. It has been used by us in very small children after digital dilatation without harm, and has afforded us visualization that was difficult if not impossible through the so-called "infant" proctoscope.

Therapy in this condition consists of daily digital dilatation, daily use of mineral oil, or a mineral oil emulsion, to soften the stool, training to gain regular bowel habits, and the use of enemas only when absolutely necessary.

16. Inserted Foreign Body.—This is the first of five lower intestinal causes for rectal bleeding that are associated with pain. The reason is obvious, when one considers the effect of a stone or pin or other foreign body upon the mucosa of the rectum. The character of the bleeding—bright, on the stool, small in amount, and often with pain—is easily understood.

Removal of the foreign body through a proctoscope is usually sufficient treatment.

17. Fistula-in-ano.—Occasionally, a fistula-in-ano can give bleeding from the rectum if there is a large enough internal opening at the dentate line. As the stool passes, it mechanically squeezes blood from the fistulous tract. The cause is readily evident by local examination and the bleeding will be of small amount, bright, and almost always associated with pain.

Fistula-in-ano in infancy is fortunately less common than in adult life. The surgical extirpation of the fistulous tract is a simple procedure, and further care is seldom necessary.

18. Fissure-in-ano.—This is the commonest cause of rectal bleeding which a pediatrician sees. It usually follows

a series of hard stools passed with difficulty and considerable pain. A fissure is sometimes difficult to pick up unless it is quite external. Digital spreading of the anus will often reveal it, and a careful search as the proctoscope is being withdrawn will frequently be rewarding. The bleeding again is small in amount, on the stool, bright in color, and accompanied by pain. Occasionally, there will be a few drops of blood after the bowel movement.

The same therapeutic plan is followed for fissures as for chronic recurrent sigmoid intussusception, namely, dilatations, mineral oil, and regular bowel habits.

19. Hemorrhoids.—This, as a possible cause for rectal bleeding in children, is only mentioned; it is rarely found as an etiological factor.

Hemorrhoids in infancy and childhood apparently respond to methods designed to correct constipation. They are not surgical problems.

20. Rectal Prolapse.—This is an infrequent occurrence but disturbing to the parents and clinician when present. The bleeding is the result of trauma to the prolapsed mucosa so that it actually bleeds while out or, having been reduced, the stool abrades its hyperemic surface. It gives bright blood, generally on the stool, in small amounts, and is associated with pain.

Surgical therapy has not been necessary in our experience. Keeping the stool soft and strapping the buttocks together are usually efficacious. Even mildly chronic prolapse spontaneously disappears with the growth of the infant.

STUDIES

In acute rectal hemorrhage in the pediatric age group, we have instituted the following regimen. The child is seen jointly by a pediatrician and a surgeon, and a red count and hemoglobin are done, after which the child is cross-matched for transfusion. The reason for the preparation for transfusion lies in the fact that in children, especially those in infancy, a quantity as small as one ounce will correspond to a 300 to 500 c.c. loss in an adult. Bleeding and clotting times, as well as a prothrombin time, are determined. A proctoscopy is then done to see if a lower intestinal cause can be seen, provided that the hemorrhage is not so great or other signs so compelling as to indicate immediate laparotomy. Utilizing adequate intravenous replacement, the patient is watched carefully with frequent counts done as indicated. X-rays are not too helpful in these acute problems, but are employed when it is felt that they will aid in making a diagnosis. The principal decision is if and when laparotomy becomes necessary.

In chronic rectal bleeding, more time is given to a thorough investigation of etiological factors. A complete count is done, along with urinalysis and nonprotein nitrogen determination. In addition, special blood studies are made, including a platelet count, prothrombin time, bleeding, clotting, and a clot retraction time, together with a serum fibrinogen determination if indicated. The patient is proctoscoped and if all these studies reveal nothing, a barium enema and a gastrointestinal series are undertaken.

CASE FOLLOW-UP

The charts of 143 patients with rectal bleeding as the primary or accompanying complaint have been reviewed for their etiological factors. Follow-

up letters were sent to each patient's parents or a phone call made.

One hundred thirteen cases fell into one of the twenty categories discussed earlier in this paper and are listed in the order of their frequency of occurrence in Table III. The number of replies to follow-up is noted and the present positive findings recorded; only five of seventy-three replies had any such findings. All others replied that no further trouble had been encountered after hospitalization. It is of interest to note that not a single case of continued bleeding occurred in the whole group; those giving present positive findings all had difficulty with the basic disease, not with bleeding.

Nineteen of the patients had assorted conditions not usually associated with rectal bleeding, e.g., rectal vaginal fistula, megacolon, tetralogy of Fallot, meconium ileus, etc. We received seventeen replies from this group. Again none was troubled with rectal bleeding posthospitalization in the group of five who had positive findings on follow-up.

A final group of eleven in whom rectal bleeding was incidental to other lesions did not reply and were lost to follow-up.

In summary, all patients who were able to be followed were free of any further rectal bleeding. This was true whether such bleeding was their primary complaint and they were treated for it, as in Meckel's diverticulum, an intussusception or polyp, or whether the bleeding was an associated finding.

TABLE III. INCIDENCE AND FOLLOW-UP

CAUSES	CASES	REPLIES	REMARKS
Undiagnosed melena	26	20	--------
Systemic disease (Diarrhea 7, celiac 6, milk allergy 4, parasites 2, lymphoma 1, cirrhosis 1)	21	15	1 dead (cirrhosis)
Chronic recurrent sigmoid intussusception	18	6	--------
Intussusception	14	6	--------
Polyp	8	5	--------
Fissure-in-ano	8	5	--------
Meckel's diverticulum	5	5	--------
Ulcerative colitis	5	4	2 ileostomies
Volvulus	2	1	Chronic constipation
Fistula-in-ano	2	2	--------
Rectal prolapse	2	2	1 constipated without hemorrhoids
Intestinal neoplasm	1	1	--------
Hemorrhoids	1	1	--------
Total	113	73	

SUMMARY

Possible etiological factors have been considered in a child who presents himself with rectal bleeding.

A previously unreported entity, chronic recurrent sigmoidal intussusception, is described as a cause for rectal bleeding.

A basic work-up for rectal bleeding is suggested.

A series of 143 patients with rectal bleeding is reviewed as to causes and over-all prognosis.

Pediatric Profiles

C. Anderson Aldrich

(1888–1949)

DR. ALDRICH was born on March 4, 1888, in Plymouth, Massachusetts, the oldest of four sons. His Mayflower ancestry came through his mother's line, but did not interest him a great deal. His family was of moderate means, with no luxury in its background. The family moved to Boston when he was a young boy, where an uncle, a judge of the Juvenile Court of Brookline, was one of his favorite relatives and was a great influence in his life. For business reasons the family moved to New York City, where Andy received his elementary-school education. Trained in Boston to speak with a broad "a," and to look up from his book while reading, he drew down upon himself the enmity of the "gang" who were waiting for him after school. It was a bloody battle, but Andy won out, and after that had no difficulties. It was from one of his grade-school teachers that he learned to know and to appreciate symphonic music. While in New York, his father, a leather salesman, evidently was doing very well, as evidenced by Andy's statement that at this stage he had to feed and curry the horse that took the family for rides.

Andy's determination to study medicine dated back to an early childhood attack of diphtheria. The attending physician caught his imagination, and he never wavered in his determination some day to practice medicine. In 1904, when Andy was 16, the family moved to Chicago and settled in Evanston, where he finished high school and then attended Northwestern University. He was an outstanding basketball player and captained his team during his senior year. His father insisted that he become a businessman, and for

From the Mayo Clinic, Rochester, Minn.

two years Andy worked as a salesman. That was enough for him, and he told his father he was going to study medicine with or without his help.

So it was on his own that Andy studied medicine by running the medical bookshop with another student and by tutoring students on the North Shore. It was not an easy life, but it did not keep him from making an excellent record, as indicated by his election to Alpha Omega Alpha. He met his future wife during his college days, but it was not until some years later, when she returned to Evanston on a visit, that they came to know each other more closely.

He served his internship at the Evanston Hospital where, since there were only two interns, he became well acquainted with all the attending staff. Toward the end of Andy's intern year, Dr. Frank H. Blatchford, a general practitioner of Winnetka, offered him the position of assistant, which in the course of five years was to grow into a full partnership. With this job landed, he married Mary G. McCague on October 3, 1916, and settled down to do general practice in Winnetka and the adjacent North Shore communities. He had studied radiology with Dr. Case and, during the period from 1916 to 1921, did a considerable amount of the x-ray work at the Evanston Hospital.

It was during this same period that his love for the child was gradually developing and his resolve became manifest to stop general practice and devote his entire time to pediatrics. A recent letter from Dr. Blatchford says this of his relationship with Dr. Aldrich during this period: "Looking back on a good many years of practice, my association with Andy is one of my most pleasant memories." Dr. Aldrich always felt that his five years in general practice were an excellent preparation for his practice of pediatrics.

Immediately after his decision to limit his practice, he spent the greater part of a year studying in clinics of New York and Boston. In New York he spent most of his time with Dr. Schloss and Dr. Schroeder at the Nursery and Child's Hospital and in Boston at the Children's Hospital and the Massachusetts General Hospital. At the time, he regretted that it was impossible for him to study abroad. But conditions for study after World War I were not the same as before the war, and the pediatric clinics in the United States were vastly superior to what they were in the early years of this century.

Back in Winnetka again, after his study trip to the East, Dr. Aldrich spent three mornings working in the outpatient department of the Children's Memorial Hospital in Chicago under Dr. Brennemann, and he also worked at the Evanston Hospital and was a consulting pediatrician at the Chicago Municipal Tuberculosis Sanatorium. In 1935 he became assistant professor, in 1937 associate professor, and in 1941 full professor of pediatrics at the Northwestern University Medical School.

At the Children's Memorial Hospital he had the good fortune to work with Dr. McClure, and with him published his first paper on "The Disappearance Time of Intradermally Injected Salt Solution." This study related directly to kidney disease, led him into the study of chronic nephritis, which became his prime interest in the study and treatment of disease. He published fifteen papers on nephritis and contributed the chapter in Bren-

nemann's *System of Pediatrics* on this topic. His report on a new concept of chronic nephritis caused quite a stir at a meeting of the American Pediatric Society, and, as he put it later, "It took me one entire night to convince a couple of the old guard that I was not completely crazy."

Dr. Aldrich continued to work at the Children's Memorial Hospital in various ascending capacities from 1922 until 1941, when, on the retirement of Dr. Brennemann as chief of staff, he was appointed to this position. This full-time position gave Dr. Aldrich more time to develop his main interest: the preventive side of pediatrics. He was greatly disappointed that his plan to develop a pediatric unit of preventive care at the Children's Memorial Hospital was not possible of realization, which I think may have had something to do with his final move to Rochester, Minnesota, to take charge of the development of the Rochester Child Health Institute.

It is of some interest that my relationship with Andy and his family has been close, beginning with my call to see his eldest son, when a baby, for a temperature of 105°. Andy was much embarrassed that the fever had disappeared completely on my arrival, as recently recalled to me by Mrs. Aldrich. Our participation in the White House Conference in 1940 brought us close together, in that we were working for a program that emphasized mental and emotional health, as well as the physical side.

As a result of our work in the Conference and our frequent breakfast meetings in Chicago on my trips East, we continued to discuss how the mental and emotional side of pediatric care could be introduced and developed. The opportunity came when the Mayo Foundation decided to extend its public health research activities, and Dr. Aldrich was invited to accept the directorship of the Rochester Child Health Institute. He accepted, an action which came as a great surprise to many of his pediatric friends. I recall Andy's showing me a letter that he had received from Dr. Brennemann, in answer to his telling his former chief that he was going to Rochester. The letter contained the following: "Your interest seems to be keeping well children well, but I like mine sick," showing, inversely, the new spirit that was developing in pediatrics.

In the days of Andy's general practice, his interest centered in the youngest member of the family. As Mrs. Aldrich put it, "Andy had a genius for little babies." That was his gift which he inherited perhaps from his mother who used to say in her Yankee way, "I just love a little green baby."

Dr. Aldrich's interest spread to the older children as his patients grew up, and we find that because of that great interest he was asked by the superintendent, Carleton Washburn, to serve as a member of the Educational Council of the Winnetka schools in 1928. He served on that council until 1941, and from 1934 to 1940 he served on the school board. His suggestion agreed with the superintendent's that a psychiatrist be made available to the Winnetka schools as a preventive measure. This caused quite a furor at the time, but was accepted when the community found that this procedure really helped in maintaining the mental health of the school children.

After he had been in pediatric practice for a few years, he took care of infants during their first year for an

annual fee which included the following service: a monthly office examination, all immunizations, and as many house calls as necessary for any illness during the year. He felt it was an excellent plan to see sick patients early, and in his experience the opportunities offered by the plan were not abused by the mothers.

His interest in family relations is well illustrated by his three books, the last two of which he wrote in joint authorship with his wife, Mary: *Cultivating the Child's Appetite,* published in 1927, *Babies Are Human Beings,* published in 1938, and the third, *Feeding Our Old Fashioned Children,* published in 1941. *Babies Are Human Beings* undoubtedly was his most outstanding book, and it showed his understanding of the problem of looking at growth from the standpoint of a child. "What is he trying to do in the process of growing up?" It was an excellent book for both the pediatrician and general practitioner, and for parents, and was a good antidote to the very prevalent pediatric problem of the time, "the child that won't eat." *Babies Are Human Beings* appeared in an English edition, and in Swedish and Norwegian translations.

In addition to an active private practice and services at the Evanston Hospital and Children's Memorial Hospital, Dr. Aldrich found time to play an important role in the organization of the American Academy of Pediatries and the American Board of Pediatrics. He was one of the original small group of pediatrists who, at a meeting of the American Medical Association in Portland in 1929, saw the importance of a large, inclusive pediatric organization for furthering the care of children in the United States. As a result of this meeting, Dr. Aldrich and Dr. Abt were appointed to consult with Dr. Grulee, the secretary of the Central States Pediatric Society, at the time our largest pediatric organization. The three drew up plans of organization that were presented and accepted at the Detroit meeting of the American Medical Association. Dr. Aldrich acted as temporary secretary. He was elected the first chairman of Region III at the first meeting of the American Academy of Pediatries in Philadelphia in 1931.

From 1933 to 1944 he acted as secretary of the American Board of Pediatries. He was elected to the board by the pediatric section of the American Medical Association. He took a great interest, especially, in those physicians who failed to pass the examination, spending many hours writing them in detail what they needed to brush up on in order to pass the examination.

One characteristic incident which shows Andy's generous nature: A pediatrician from the West who had twice failed the examination wrote a very bitter letter to the board. In reply, he received a very frank letter from Andy telling him of his shortcomings, with the result that the gentleman gave up his practice, spent nine months in graduate study, and passed his third examination with flying colors. It was this frankness that was one of Andy's outstanding characteristics: his ability to tell people the truth, be it patient, parent, physician or friend, without offending him.

In 1930 Dr. Aldrich was chairman of the Section on Pediatries of the American Medical Association, and in 1944 he was president of the American

Pediatric Society. He was a member of the editorial board of *The Journal of Pediatrics* from its foundation until 1948, and he was editor of the pediatric section of *Psychosomatic Medicine* from 1940 to 1947. In 1946 Northwestern University conferred on Dr. Aldrich a "Merit award in recognition of worthy achievement." The greatest recognition of his splendid contributions came in 1948, when he was the recipient of the Lasker Award, given by the National Committee for Mental Hygiene for outstanding contributions to the education of physicians in the psychologic aspects of the practice of medicine.

Until Dr. Aldrich went to Rochester in 1944, he had published some sixty-six articles, about equally divided between the treatment and the prevention of disease, whereas during his five years in Rochester he had fifty-seven publications, all but one of which were on the development of health procedures and the prevention of disease.

On his arrival in Rochester he had the opportunity to outline and develop a program of child care for an entire community, the first study of this kind ever attempted. He gathered together a superb staff which, added to the available health facilities of the sections of pediatrics, psychiatry, and obstetrics of the Mayo Clinic, the Rochester City Department of Health, and school and county nurses, made an ideal setting for such a study. As the study progressed, it evoked great national, as well as international, interest. In the year 1949, ninety-six individuals from outside the United States came to Rochester to visit the Rochester Child Health Institute, and they, together with the many guests from this country, made visitors a new service to reckon with. Just one quotation from the report of the experts on the Committee on Mental Health of the World Health Organization to show the value placed on this study: "Such work as the Rochester Child Health Institute is carrying on and the recommendation for its development elsewhere would be a fitting subject for action by the World Health Organization."

The program of the Rochester Child Health Institute was planned as a longitudinal study, for at least twenty years in duration. During the first five years it grew so rapidly, and the voluntary cooperation of the parents of the community was so wholehearted, that it was not always easy to keep it within the bounds of the purely preventive program, on which basis it was set up.

In 1948 an acute illness developed which temporarily kept Dr. Aldrich from his work. A rapid recovery and gain in strength and weight were followed a year later by more serious symptoms. Surgical exploration revealed an inoperable tumor of the pancreas. He lived on for six months, with the constant worry of what would happen to "the project."

Dr. Aldrich was a man of the highest ideals, a man willing to make any necessary sacrifice to attain what he considered his aim and possible life's accomplishment. His willingness to give up one of the outstanding positions in pediatrics in America to accept the Rochester position so that he could pursue his quest of the perfect setting for all children shows what he was willing to sacrifice for an ideal. He cared deeply about what happened to children, to all children. He was an

idealist in whom there was combined a great deal of tolerance. It was my privilege to know Andy more intimately in his last years here in Rochester, and no better friend than Andy did any man ever have.

Dr. Aldrich left behind him his wife, Mary, a grand helpmate in his work; a daughter, Cynthia; and two sons, Dr. Robert A., now associate professor of pediatries in the University of Oregon Medical School; and Dr. Stephen L., now serving with the Army in Japan.

The broad basis of Dr. Aldrich's pediatric concept is perhaps best illustrated by a quotation of the final lines from his article, "The Significance of a Complete Preventive Medical Program for Children": "We live in a democracy which we are fighting to preserve. The children now growing up will be its leaders of the future, but we cannot expect to have successful leaders in a democracy unless they are emotionally stable enough to stand on their own feet and give and take freely with their fellowmen. This required emotional stability must stem from a basic security and confidence, the kind that grows up from childhood. It does not seem impossible that human nature may have more cooperative aspects than we have hitherto thought possible. We can make a start at finding this out by applying the wholesome principles of growth to infant and child care."

Henry F. Helmholz

Comments on Current Literature

STAPHYLOCOCCIC INFECTIONS OF THE NEWBORN INFANT

THE occurrence of pathogenic staphylococci in the environment of the newborn infant has prompted a number of investigations concerning the role of these microorganisms in morbidity and mortality among infants of the newborn period. In 1954 Hardyment[1] reviewed staff experiences at the Vancouver General Hospital, reporting some interesting statistics. In the year 1952 there were 4,639 infants born alive. Eight of these newborn babies died of infection. In six of the eight, the presence of pneumonia was reported at the time of autopsy. Apparent skin infection occurred in 114 of the 4,639 infants, oral thrush in 47, conjunctivitis in 36, acute respiratory infection in 7, omphalitis in 4, diarrhea in 3, in 1 furunculosis, and paronychiae, mastitis, and meningitis, in 1 each, respectively. Thus a total of 215 newborn infants was presumed to have become infected in the nurseries over a twelve-month period.

General bacteriologic culture studies of the nose in newborn infants have revealed that at the end of the first day of life about 9 per cent of neonates in general have pathogenic staphylococci in their noses, as high as 50 per cent by the end of the second day, and about 80 per cent between the fourth and eighth days of life. *Staphylococcus aureus* is often prevalent in the noses of hospital personnel.

About the same time as the investigation in Vancouver, Webb[2] undertook a study of the role of pathogenic staphylococci in newborn infections in two hospitals in Winnipeg, Canada. In one of these hospitals, in which there were 585 live births, the incidence of skin infection was of the order of 9 per cent (53 in 585 newborn infants). During this same period, somewhat over 5 per cent of the mothers had breast abscesses. It was interesting that the outbreak of infection in one of these institutions was associated with only two known carriers, whereas in the other hospital eleven carriers were detected. Webb emphasized the elimination of chronic carriers of staphylococci from the nursery environment as a fundamental procedure in the control of any outbreak, and stated that "hospital facilities and particularly the quality of nursing care are very important factors in limiting the spread of infection in hospitals."

In the March 19, 1955, issue of *Lancet,* Forfar and his associates[3] of Edinburgh, Scotland, report their experiences with staphylococcal infections of the newborn infant. In their study, 50 to 80 per cent of the hospital strains of *Staphylococcus pyo-*

genes isolated were resistant to penicillin, and in their opinion resistance of these microorganisms to the tetracyclines is increasing. Two outbreaks were studied by Forfar and his co-workers. In one hospital during a nine-month period of close observation, the incidence of clinical infection was 14 per cent, in another hospital, 13 per cent. In one of these institutions, a total of 140 infants was shown to be infected with strains of staphylococcus during the nine-months period: 64 per cent, conjunctivitis; 14 per cent, skin pustules; 9 per cent, infection of the umbilical stump; and 6 per cent, local cellulitis or paronychia. The remaining 7 per cent were not well documented. In the second hospital studied during this period, 120 infected infants were distributed clinically as follows: 61 per cent, conjunctivitis; 24 per cent, skin pustules; 4 per cent, umbilical stump infections; and cellulitis or paronychia in 11 per cent. These authors concluded that there is a free exchange of staphylococci between staff and infants, and between the infants themselves. Good therapeutic results were obtained with erythromycin alone, or in combination with streptomycin; chloramphenicol was used locally in the eyes.

The *British Medical Journal*[4] for April 23, 1955, carries a second report of studies conducted by the Edinburgh investigators. Medical, nursing, and domestic personnel were checked as possible disseminators in three maternity units in Edinburgh; 51 per cent of these personnel were shown to be carrying *Staph. pyogenes* in the anterior nares. A careful bacteriologic study of the strains isolated showed that 58 per cent of them were completely resistant to penicillin, and 20 per cent completely resistant to the sulfonamides. Less than 10 per cent proved resistant to chloramphenicol, chlortetracycline, and streptomycin. So far as the mothers were concerned, only the vaginal carrier rate, which was insignificantly low at delivery, rose during the following eight-day period, whereas in the case of the infants, the eye carrier rate rose to 35 per cent on the fourth day, and the umbilical carrier rate to 40 per cent on the eighth day. Carrier rates for babies born at home were considerably less: 5 per cent on the fourth day after delivery and 8.6 per cent on the eighth day after delivery. The authors concluded that the incidence of penicillin-resistant strains of *Staph. pyogenes* is much higher among nurses and babies than among mothers, and higher in week-old infants born in the hospital than in those born at home. In this second series reported from the Edinburgh hospitals, the infections comprised relatively mild skin conditions and conjunctival sepsis, with almost complete absence of serious infections.

A striking clinical manifestation of infection with *Staph. pyogenes aureus* is being described, namely, acute mastitis of the newborn infant. Moseley[5] has reported in the *United States Armed Forces Medical Journal* that of 665 infants born over a seven-month period, 14, or 2 per cent, developed acute mastitis, 2 of them within less than five days after discharge from the hospital. These abscesses appeared in the area beneath the breast tissue, the infection apparently having no connection with the breast ducts proper. Among

these fourteen neonates with mastitis four were shown to have throat cultures positive for this organism at the same time as the breast abscesses. It has been estimated that about 62 per cent of healthy newborn infants will show positive throat cultures for staphylococcus strains.[6] Among the newborn infants with mastitis reported by Moseley was one instance of local trauma which might account for localization of the infection in the infant's breast. These patients with mastitis were treated with warm moist compresses, and antibiotic therapy before and after surgery. Surgical drainage was required in all fourteen instances. The author stresses the fact that 75 per cent of the strains of *Staph. pyogenes aureus* encountered in this series of patients were resistant to penicillin; many proved to be sensitive to Aureomycin and to Terramycin.

The presence of pathogenic staphylococci in the environment of the susceptible newborn infant, particularly the premature infant, has been emphasized in many reports. The increasing number of strains becoming resistant to antibiotics, notably penicillin, magnifies the seriousness of this problem. Efforts to prevent the spread of pathogenic organisms to neonates must be redoubled. Careful scrutiny of the health of nursery personnel, intelligent epidemiologic studies for the presence of staphylococci, prompt recognition of sepsis in the newborn infant with immediate isolation of the baby in a suspect nursery, and prompt and effective treatment of early clinical manifestations of neonatal sepsis are needed in order to reduce morbidity and mortality rates in this important and peculiarly vulnerable pediatric age group.

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News and Notes

Dr. Franklin P. Gengenbach of Denver died August 29, 1955, following an illness of several years. He would have been 80 years old in October. Dr. Gengenbach was a pioneer pediatrician in the Rocky Mountain area and the first in that region to limit his practice to children. He was a Philadelphian by birth and received his M.D. degree from the University of Pennsylvania in 1899. He interned at St. Christopher's Hospital for Children in Philadelphia, later did postgraduate work at the Children's Hospital in Boston, and studied in Berlin and Vienna. For many years he was professor of pediatrics at the University of Colorado Medical School, and was one of the organizers of the Children's Hospital in Denver, serving on its staff from 1910 until his retirement in 1946.

He was a member of the American Pediatric Society, and one of the Founder group of the American Academy of Pediatrics, serving as president in 1943. In 1918 he was chairman of the Section on Pediatrics of the American Medical Association, and for a number of years was a member of the American Board of Pediatrics. In World War I he was a Captain in the Medical Corps, United States Army.

He was a genial, happy man who had hosts of friends throughout the country.

Dr. Blair E. Batson has been named professor of pediatrics and chairman of the department of pediatrics at the University of Mississippi School of Medicine. For the past year he has been assistant professor in both child health and pediatrics at Johns Hopkins.

Dr. Henry B. Strenge of Oklahoma City has been appointed full-time head of the department of pediatrics at the University of Oklahoma.

Dr. Frank Falkner has been appointed assistant professor of child health at the University of Louisville. Dr. Falkner is at present lecturer in child health, the Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London; and research assistant to that Hospital. He is also coordination officer to the Centre International de l'Enfance, Paris, for their coordinated growth studies. These studies, taking place in different countries have, as yet, no North American member of the "group." It will be part of Dr. Falkner's duties to set up such a cooperating growth study in Kentucky.

A Fellowship in *Pediatric Neurology* is available at the Children's Neurology Clinic of the Cook County Hospital in Chicago. The Fellowship will provide clinical training in the diagnosis and rehabilitation of children with neuromuscular handicaps. In addition the trainee will be expected to participate in a clinical laboratory problem. The annual stipend will vary from $3,000 to $5,000, depending upon the qualifications of the applicant. For further information write M. A. Perlstein, M.D., 4743 N. Drake Ave., Chicago 25, Ill.

A Fellowship in *Pediatric Cardiology* under the auspices of the American Heart Association (Colorado Chapter) is now available at the Children's Hospital in Denver. Facilities and supervision are excellent; clinical material is abundant. Children's Hospital is a 210-bed, fully accredited institution that has been actively engaged in cardiac diagnosis and treatment for many years. Graduates of Class A medical schools who have satisfactorily completed one or two years of hospital work are eligible. The stipend is $3,600 per annum. Communicate

at once with the Director, Cardio-Pulmonary Laboratory, Children's Hospital, Denver 18, Colo.

Director, Maternal-Child Health, Pennsylvania Health Department. Nationwide open competitive merit system position, $10,260 to $12,108. Directs statewide program, maternal-child health. For information and applications, write to State Civil Service Commission, Box 569, Harrisburg, before final filing date of November 25, 1955.

The Second Congress of the World Confederation for Physical Therapy will be held at the Hotel Statler, in New York City, June 17 to 23, 1956.

Books

La progénèse. Paris, 1955, Masson et Cie, 720 pages. Price 3,500 francs (Fr.).

This is an unusual and interesting book. It consists of the discussions or lectures presented at a course given by the International Center for Infancy in Paris in 1954, under the direction of Prof. Raymond Turpin of the faculty of medicine in Paris. We know of no other such complete discussion of the effects of preconceptional factors on the development of the infant. It goes into factors far beyond the usual genetic discussion of the theme. The first section takes up the biological basis of progenesis; the second on progenesis and population contains discussions of such factors as patrimony, human hybridization, and the influence of geography; the third part contains discussions of the part played by heredity in specific diseases of the various systems; the fourth, individual factors such as the effect of previous infections and toxic agents on the genes; a fifth and final section takes up social factors as the structure of society on the evolution of population, and moral and religious concepts. There is an excellent bibliography to the sections without much specific reference in the presentations.

Over thirty have participated in the presentation of the forty-six chapters or lectures in the course. Most were members of the faculty of medicine of Paris, but others have been called on to present specific subjects, as Van Bogaert of the Bunge Institute at Antwerp, and J. B. S. Haldane and P. L. Mollison of London. The text summarizes a vast amount of knowledge and literature, and those who read French without too much difficulty will find it interesting and profitable reading.

The Emotional Problems of Children. A Guide for Parents. Harry Joseph, M.D., and Gordon Zern, New York, 1954, Crown Publishers, Inc., 310 pages. Price $3.75.

A text for parents by the Director of the Guidance Center of New Rochelle, who is an advocate of the Freud philosophy and methods. The book discusses many of the practical problems of an emotional nature in childhood. The great question of this and similar texts is whether they will not confuse rather than help the parent who tries to interpret and correct the problem by following textbook advice.

Obstetrics, ed. 11. J. P. Greenhill, M.D., Philadelphia, 1955, W. B. Saunders Co., 1088 pages. Price $14.00

The foreword states that the entire book has been rewritten since the last edition in 1951. In going through it to note the parts of chief interest to the pediatrician, we find that much of the section on the physiology of the newborn infant is direct quotation by permission from the text by Clement A. Smith. In his discussion of postmaturity the author disagrees with the importance attached to this subject by Stewart A. Clifford. The discussion of erythroblastosis and the Rh factor is clear and practical.

The Postnatal Development of the Human Cerebral Cortex. Vol. V. The Cortex of the Fifteen-Month Infant. J. LeRoy

Conel, Cambridge, Mass., Harvard University Press, 214 pages plus 100 plates. Price $12.50.

The fifth volume of the development of the human cerebral cortex describes the development at the fifteenth month level. Like the earlier volumes, it is beautifully illustrated. It will be of chief interest to the anatomist and neuropathologist.

A Textook af Medicine, ed. 9. Edited by Russell L. Cecil, M.D., and Robert F. Loeb, M.D., Philadelphia, 1955, W. B. Saunders Co., 1786 pages. Price $15.00.

A new edition of Cecil and Loeb's well-known text. There are over 150 contributors to this rather encyclopedic reference text, and in the ninth edition between forty and fifty new subjects are introduced for the first time.

Ageing—General Aspects. Edited by G. E. W. Wolstenholme and Margaret P. Cameron, Boston, 1955, Little, Brown & Co., 255 pages. Price $6.75.

Papers and discussion of a "Colloquia on Ageing" held in London in 1954 by the Ciba Foundation under the chairmanship of Prof. R. E. Tunbridge of the University of Leeds. Some thirty-five interested in and working in the field of geriatrics took part.

Surgical Forum. Proceedings of the Fortieth Clinical Congress of the American College of Surgeons in 1954. Philadelphia, 1955, W. B. Saunders Co., 851 pages. Price $10.00.

A collection of over 150 papers presented at the Forum which covers the advances in the entire field of surgery.

Sexual Hygiene and Pathology. John F. Oliven, M.D., Philadelphia, 1955, J. B. Lippincott Co., 481 pages. Price $10.00.

A straightforward discussion of sexual hygiene and pathology for the physician by the psychiatrist to the Vanderbilt Clinic of the Columbia-Presbyterian Medical Center in New York.

The Practice of Dynamic Psychiatry. Jules H. Masserman, M.D., Philadelphia, 1955, W. B. Saunders Co., 790 pages. Price $12.00.

This text will be of interest to those working in the field of child psychiatry rather than the pediatrician in practice. It extends the application of "biodynamics," a system which the author presented a few years ago in his text, *Principles of Dynamic Psychiatry*, to clinical psychiatry.

Untersuchung und Beurteilung des Herzkranken. Prof. Dr. H. W. Knipping, Doz. Dr. W. Bolt, Dr. H. Valentin, and Dr. H. Venrath, Stuttgart, 1955, Ferdinand Enke Verlag, 461 pages. Price D.M. 83.

A text from the University Clinic at Cologne which discusses practical routine diagnosis and preoperative diagnostic methods.

Clinical Toxicology, ed. 3. Clinton H. Thienes, M.D., and Thomas J. Haley, Ph.D., Philadelphia, 1955, Lea & Febiger, 457 pages.

Editor's Column

COUNSELING IN HUMAN GENETICS

ALTHOUGH heredity has been a subject of speculation and discussion since Biblical times, it was not until a century ago that the studies of the Austrian monk, Gregor Mendel, placed genetics on a scientific basis. As a matter of fact, our scientific knowledge of human genetics dates from around the beginning of the present century when Mendel's work was "rediscovered." Since then the literature on the subject has become voluminous and the genetic background of many traits and diseases has been worked out. Many of the discussions are extremely technical and leave the average physician somewhat bewildered. However, it is to their physician that most people turn for help when bothered by a problem they feel may involve hereditary transmission.

Late in August a relatively small and unusually interesting and readable book came to the Editor's desk, entitled *Counseling in Human Genetics*. The author, Dr. Sheldon C. Reed, is Director of the Dight Institute for Human Genetics at the University of Minnesota. We were quite unaware that there are thirteen "Heredity Clinics" in the United States and Canada which offer counseling in genetic problems to physicians, the public, and social agencies. Dr. Reed, the principal counselor at the Dight Institute, has taken as the basis of his book the twenty most common causes which have led to requests at his clinic. The first ten of these in order of frequency were (1) skin color, (2) epilepsy, (3) consanguinity, (4) mental deficiency and mongolism, (5) schizophrenia, (6) harelip and cleft palate, (7) eye color, (8) twinning, (9) rhesus factor and erythroblastosis, (10) cancer. To chapters covering each of the twenty subjects he has added a few more including body type, tuberculosis, and pyloric stenosis. The order of frequency of the requests in no way represents the relative frequency of the genetic trait in the population, but rather gives a picture of what the public is most interested in and bothered about. There are a great many other conditions and diseases with a genetic relationship, and to cover these the author has republished as an appendix the data which appeared in the January, 1954, issue of THE JOURNAL OF PEDIATRICS in a discussion of *Medical Genetics in Pediatrics* by Dr. F. C. Fraser of Montreal. The chapters in the book are brief and to the point, and summarize what is known in regard to the particular condition. References are given to more extensive discussions of each condition in case the physician wishes to go more deeply and technically into a specific condition. A number of these references are to the discussions in a recent English text on

Clinical Genetics edited by Dr. Sorsby.* Not the least interesting part of Dr. Reed's discussions are the examples of the requests received by the clinic and the reply, which follows each chapter. The author stresses a point which the physician whose advice or counsel is sought might well heed. The person giving counsel should not tell people what or what not to do in a given situation. His function is to present the known facts and probabilities, but the decision must be left to those asking advice.

Genetics is of steadily increasing importance in medical practice, as a result of the scientific developments in therapy. An example is diabetes. Insulin has lessened the morbidity of the disease and increased the population capable of transmitting the diabetes gene. A recent English study* on pyloric stenosis found that 10 per cent of the infants born to parents who survived the condition following a Ramstedt operation in 1920 to 1929 developed the disease. What effect the more recent antibiotics will have on genetic diseases is at present only a matter for speculation. Because genetics is a subject which is becoming of steadily increasing importance in medical practice, Dr. Reed's very readable book is of unusual interest.

*Clinical Genetics, St. Louis, 1953, The C. V. Mosby Co.

*Carter, C. O., and Powell, B. W.: Two-Generation Pyloric Stenosis, Lancet 266: 746, 1954.

Ahead of His Time

In the Amoenitates Academiae, there is a curious dissertation on this subject, where the author attempts to prove that living small animalculae, lodged in the intestines, are the cause of dysentery; but as we have no evidence of these, we must consider the theory as merely an hypothesis, or the chimera of a fanciful imagination.

From David G. Abeel, Inaugural Dissertation on Dysentery, New York, 1794.